Tackling Early Morbidity and Mortality in Myeloma: Assessing the benefit of antibiotic prophylaxis and its effect on healthcare associated infections (*TEAMM*)

Chief Investigator

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Authorised Signature _____

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LIST OF ABBREVIATIONS

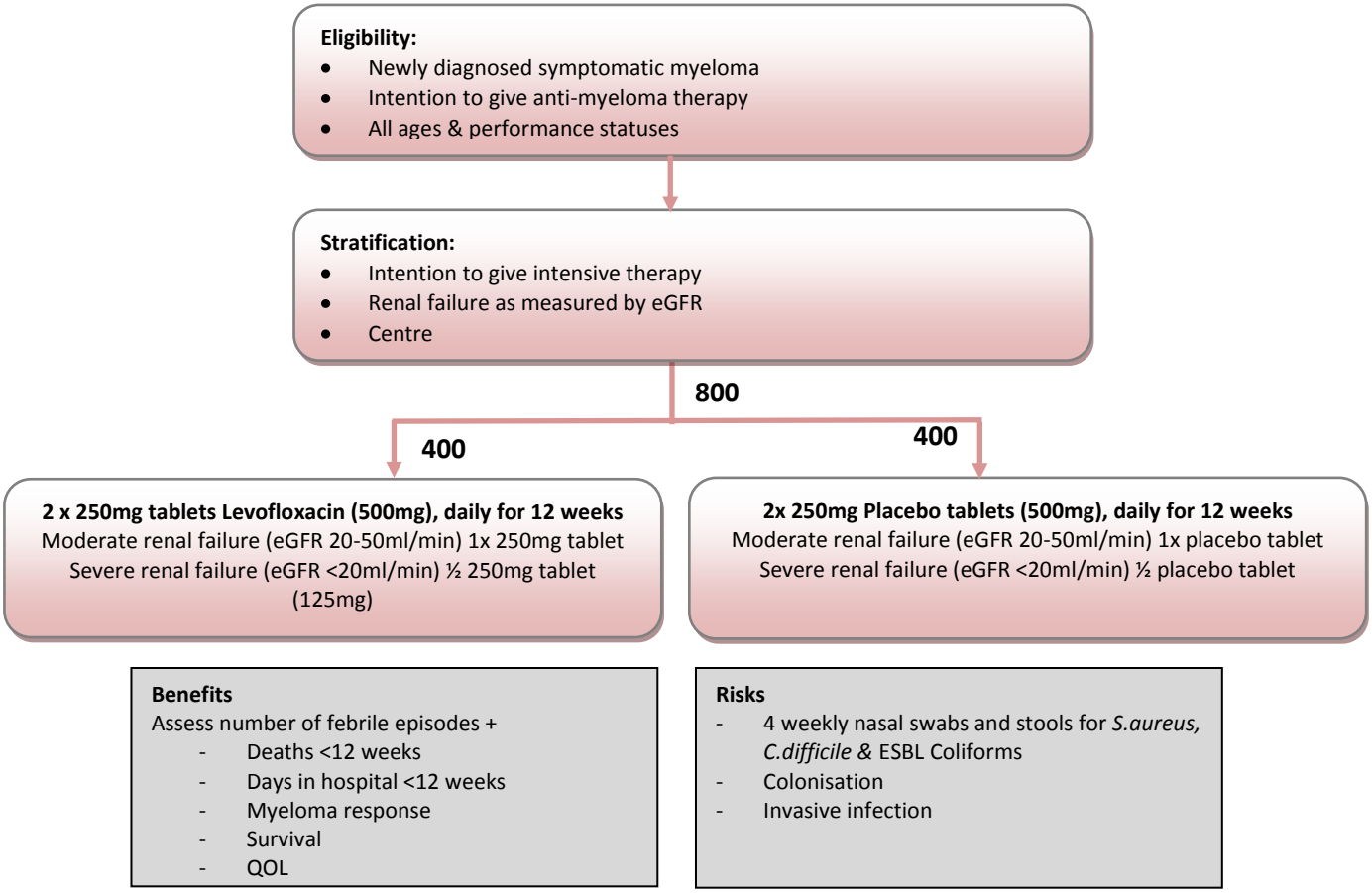
Abbreviation	Explanation
AE	Adverse event
CRF	Case Report Form
CTU	Clinical Trials Unit
DMEC	Data Monitoring and Ethics Committee
GCP	Good Clinical Practice
ICH	International Conference on Harmonisation
MREC	Multicentre Research Ethics Committee
QOL	Quality of Life
R&D	Research and Development
SAE	Serious adverse event
SAR	Serious adverse reaction
SOP	Standard Operating Procedure
SUSAR	suspected unexpected serious adverse reaction
TSC	Trial Steering Committee
WCTU	Warwick Clinical Trials Unit

Table of Contents

1. Trial Summary

Title:	**Tackling Early Morbidity and Mortality in Myeloma: Assessing the benefit of antibiotic prophylaxis and its effect on healthcare associated infections (*TEAMM*)**
Rationale:	Myeloma is a cancer of bone marrow plasma cells that causes profound immunosuppression. There is a high early death rate with the biggest single cause being infection. Recent improvements in overall survival in myeloma mean that prevention of early death has become more pressing, especially as early death affects all prognosis groups. Antibiotic prophylaxis is likely to be the single most effective measure to prevent early death in myeloma. Treatment with antibiotics once an infection is established is probably not sufficient, as the early death rate in older patients remained constant over a 20 year period despite improvements in supportive care. The use of antibiotic prophylaxis is evidence based established practice in some areas of medicine, e.g. neutropenia, HIV, but the recent rise in healthcare associated infections (HCAI) has raised concern about the risks of antibiotic prophylaxis. Although the benefits are well established, there is concern that clinicians are withholding antibiotic prophylaxis because of fears of HCAI. Extrapolating from current data the benefits of prophylaxis are likely to outweigh the risks of HCAI. However there has not been a large trial looking at the benefits of antibiotic prophylaxis versus the risks of HCAI. Examination of the organisms causing infection in myeloma suggests that Levofloxacin, given for the first 12 weeks, is the best antibiotic for prophylaxis. Reducing infection in the first 3 months may increase the myeloma response rate primarily by reducing the number of interruptions of anti-myeloma therapy. There is also some evidence for a role for infections driving myeloma pathogenesis directly although further proof is required to confirm this effect in vivo.
Eligibility Criteria:	**Patients with the following characteristics are eligible for this trial:** • Age ≥ 21 years and able to give informed consent • Patient with newly diagnosed symptomatic myeloma based on internationally agreed criteria • Patient is no more than 7 days into starting a programme of anti-myeloma therapy or no more than 14 days into starting anti-myeloma therapy if already on a broad spectrum antibacterial agent. *(Patients are eligible to be randomised prior to commencement of anti-myeloma therapy if they have an anticipated anti-myeloma therapy start date and that the trial drug is commenced within the 7 days prior or 7 days after commencing their anti-myeloma therapy)* • Provision of written informed consent
Exclusion Criteria:	**Patients with the following characteristics are ineligible for this trial:** • Patients with contraindication to Levofloxacin:- - known to have sensitivity / allergy to Levofloxacin or other quinolones - Patients with a history of tendon disorders related to fluoroquinolone administration - Patients receiving other prophylactic antibiotic treatment (excluding pneumocystis prophylaxis if regarded as essential) - Patients receiving amiodarone or arsenic trioxide - Patients on active antiepileptic treatment • Women of childbearing age who are not willing to use appropriate methods of contraception to prevent pregnancy or women that are breastfeeding

	• Patient thought to have mandatory requirement for prophylactic antibiotics • Patient who is not going to receive anti myeloma therapy
Objective:	To assess the risks, benefits and cost effectiveness of levofloxacin in newly diagnosed symptomatic myeloma by a prospective, multi-centre, randomized, double-blind, placebo controlled trial.
Trial Design:	*TEAMM* is a randomized, double-blind, placebo-controlled multi-centre phase III clinical trial assessing the benefit of antibiotic prophylaxis and its effect on health care associated infections.
Treatment:	**Experimental arm:** Levofloxacin 500 mg once daily orally for 12 weeks. **Control Arm:** Placebo once daily orally for 12 weeks. All patients will receive Anti-myeloma therapy.
Number of patients:	800
Sample Collection:	At entry, 4, 8, 12 & 16 weeks central laboratory analysis of stools and nasal swabs for microbiology; blood and urine for paraprotein response and immune function
Sub-study assessments:	Quality of Life (EQ-5D, EORTC-QLQ C30 and The Hospital Anxiety & Depression scale HADS) and Heath Economics which will be administered via a daily patient diary.
Stratification:	• Centre • Intention to give high dose chemotherapy with stem cell rescue • Renal Failure as measured by eGFR



2. Background

Epidemiology and burden of the condition

Myeloma is a cancer of bone marrow plasma cells that causes anaemia, skeletal fractures, renal failure and profound immunodeficiency. There are approximately 4,000 new UK cases of myeloma per annum (Cancer Research UK). The overall prevalence however is likely to be increasing given the recently published data demonstrating improved survival rates over the last decade (Kumar *et al,* 2008; Brenner et al, 2009). 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 (Bird et al 2009). The majority of cases present *de novo* but it is now recognised that this is preceded by an asymptomatic MGUS phase in virtually all patients (Landgren *et al,* 2009).

Myeloma causes profound immunodeficiency and recurrent, serious infections. A quarter of patients will have a serious infection within 3 months of diagnosis. Ten percent of patients die within the first 60 days of diagnosis, with bacterial infection directly causing 45% of these deaths. Recent advances in anti-myeloma therapy have improved overall survival significantly, yet this high early death rate remains little changed, affecting all prognostic groups. Patients who may have had long term survival with current anti-myeloma therapy are dying soon after diagnosis, from bacterial infection. Newly diagnosed myeloma patients may therefore benefit from antibacterial prophylaxis to prevent infection, hospital admission and early death. Reducing infection may also improve response to anti-myeloma therapy by reducing interruptions of anti-myeloma therapy and reducing immune responses to infection that promote myeloma cell survival and growth. In patients with other causes of immunodeficiency such as neutropenia, asplenia, HIV and reflux nephropathy, the importance of prophylactic antibiotics to prevent infection is well established and common practice in the NHS. However the use of prophylaxis has not been established in myeloma. Furthermore some of the studies that established the use of antibacterial prophylaxis in other conditions predate the current rise in healthcare-associated infections (HCAI), such as *Clostridium difficile*. The data from these older trials may not reflect current risks associated with antibiotic prophylaxis and so there is a need to reassess the affect of antibiotic prophylaxis on HCAI.

Existing knowledge

Large studies in Europe and North America have identified a high mortality (8-20%) in the first 3 months from diagnosis of myeloma, with bacterial infection being the single biggest identifiable cause (Perri et al, 1981; Lenhoff et al, 2000; Blade et al, 2001; Augustson et al 2005). An analysis of 3107 myeloma patients registered onto UK MRC trials from 1980 to 2002 showed that 10% of patients died within 60 days of trial entry and 45% of these deaths were directly due to bacterial infection (Augustson et al, 2005).

In the "MRC myeloma 9" trial recruiting between 2003 and 2008 overall incidence of infection in non-intensively treated patients was 214/692 (30.9%) with median time to infection from first diagnosis of myeloma of 43 days. Recent advances in anti-myeloma therapy have improved survival significantly, yet this high early death rate remains unchanged over 30 years and affects all prognosis groups. This suggests current supportive care strategies including the treatment of an infection once established, may be insufficient. *Streptococcus pneumoniae*, *Staphylococcus aureus* and *Escherichia coli* are the most frequent types of bacterial infection in myeloma patients (Cohen and Rundles 1975; Savage et al, 1982; Esperesen et al 1984; Jacobson and Zolla-Pazner, 1986; Doughney et al 1988; Rayner et al, 1991). The risk of these infections is associated with myeloma disease activity and abates as the disease is brought under control with anti-myeloma therapy.

The mechanism by which the risk of infection is increased in the presence of active myeloma disease is not well understood. Over 90% of 2695 MRC myeloma trial patients had reduced levels of normal antibodies and these patients susceptibility to bacterial chest infections is characteristic of antibody deficiency. However a previous MRC trial of IgG replacement therapy (double blind randomised placebo controlled of 203 patients) did not significantly reduce mortality or morbidity from infection in the first three months from diagnosis despite effectively increasing total serum IgG levels and titres against specific bacterial pathogens. Myeloma patients are not usually neutropenic at presentation and only 11 of 135 myeloma patients dying of infection

within 60 days of diagnosis had a neutrophil count less than 2.0 x 10^9 /l (Augustson et al 2005). Other factors associated with active myeloma disease that might increase risk of infection include low serum complement C4 levels, increased TGF beta and increased IL-10 (Pratt et al 2007).

Antibacterial prophylaxis is an obvious strategy to prevent infection, hospital admission and early death in these patients. Of the only 2 trials of prophylactic antibiotics in early myeloma, one prospective randomised study was with co-trimoxazole in the early 1990s (Oken MM et al, 1996). This showed a reduction in bacterial infections with prophylactic Co-Trimoxazole (2/28 treated vs 11/26 control patients) and was too small to detect reduced mortality. A recent trial of 212 patients given Ciprofloxacin, Co-trimoxazole and placebo showed no difference in the rate of infection (Vesole DH et al, 2010). This study was again underpowered to show differences in infection and mortality. The low incidence of all infections (22%) in this study raises the question as to whether the patients were representative of the normal myeloma clinic population. Offidani et al (2011) on retrospective analysis of infections in 202 patients on new therapies found 40% patients had an infection within 6 months, with 80% of severe infections (16% of patients) occurring in the first cycle of treatment. Antibiotic prophylaxis was effective in preventing infections in those patients with surrogate markers of high tumour burden (monoclonal band >3g/dl, platelet count <130 x10*/l) but not in those without these parameters.

Antibiotic prophylaxis should be active against the bacteria commonly causing infections in the patients treated, ideally oral once daily medication to maximise adherence and efficacy, and have few side effects. For all the above reasons the quinolones, particularly ciprofloxacin and levofloxacin are now the most commonly used antibiotics for chemoprophylaxis.

Although less than a tenth of myeloma patients dying of infection are neutropenic (Augustson et al 2005) the immunosuppressed state in both neutropenic and early myeloma patients leads to bacterial infection. The common organisms causing infection in myeloma are *Escherichia coli, Streptococcus pneumoniae*, *Klebsiella* Spp, *Staphylococcus aureus*, *Pseudomonas* Spp, *Haemophilus* Spp. and *Proteus* Spp. These are similar to those organisms seen in neutropenic infections although gram negative infections are commoner in neutropenia. Thus studies on the use of prophylactic antibiotics active against the common pathogens that cause infection in neutropenia are pertinent to myeloma patients.

A large meta-analysis (Gafter-Gvili et al 2009) including 162 studies with 12,599 neutropenic patients showed that all antibiotic prophylaxis significantly reduced the risk for death compared with placebo or no treatment (relative risk (RR) 0.66 [95% CI 0.55 to 0.79]). Fluoroquinolone prophylaxis was the most effective and reduced the risk for all-cause mortality (RR 0.52 [CI, 0.37-0.74], as well as infection-related mortality, fever, clinically documented infection, and microbiologically documented infections. Fluoroquinolone prophylaxis increased the risk for adverse events
(RR 1.52 (95% CI 0.79 to 2.92), but these were minor events. The benefit of reduction in infection-ralated mortality, RR 0.49 (95% CI 0.31 to 0.77) far outweighed any mortality from adverse effects since all-cause mortality was still markedly reduced (RR 0.52 [CI, 0.37-0.74]. These studies translate into a number needed to treat in order to prevent 1 death from all causes in neutropenic patients as 50 (95% CI 34 to 268).

To date, only two studies have reported differences in costs and both showed a cost benefit for prophylaxis. These have focused on individual resource use elements such as the total cost of antibiotics (Buccaneve et al 2005) or hospital inpatient days (Cullen et al 2005). None of the trials included a comprehensive cost analysis or a full economic evaluation.

Levofloxacin prophylaxis may in addition to preventing infection, improve response to anti-myeloma therapy. Delivery of anti-myeloma therapy is often delayed by infection and so reducing infectious episodes may increase the amount of anti-myeloma therapy given. There is epidemiological and laboratory evidence that the cytokines and inflammatory mediators associated with bacterial infection may promote the growth of myeloma cells (Pratt et al 2007). By reducing infections antibiotic prophylaxis may reduce myeloma growth and potentiate response to anti-myeloma therapy. This will be the first study to asses these factors.

Quinolones, however, along with other antibiotics, are implicated in increased risk of colonisation with antibiotic resistant bacteria and invasive infection by those bacteria. These healthcare-associated infections

(HCAI) have been an ever increasing problem to the NHS over the last 10 years accounting for significant morbidity and mortality. Up to 1 in 4 people carry *S. aureus* and *C. difficile* may be carried by 1% to 3% of healthy people. Up to 30 % of long term hospitalised patients may carry *C. difficile*. There were 36,095 cases of *C. difficile* associated diarrhoea in the UK in 2008-2009.

There is an increasing perception that antibiotic prophylaxis will increase numbers of healthcare associated infections. A Midlands survey showed that with conventional myeloma chemotherapy 24 haematologists did not use antibiotic prophylaxis and 8 haematologists used it in selected patients. With intensive myeloma chemotherapy half of the haematologists routinely used antibiotic prophylaxis. 2009 guidelines for the diagnosis and management of multiple myeloma published by the UK Myeloma Forum (UKMF) on behalf of the British Committee for Standards in Haematology (BCSH) state 'there is insufficient evidence to recommend the routine use of prophylactic antibiotics (Grade C recommendation; level IV evidence)'.

There are insufficient data on the relationship between changes in carriage rate of potentially pathogenic organisms during antibiotic therapy and the risk of subsequent infection with the same organism. From meta-analysis on antibiotic prophylaxis trials in neutropenia, there was no significant increase in C. difficile infection (7/1250 patients receiving a Fluoroquinolone prophylaxis versus 5/1279 on placebo or no treatment) (Leibovici 2006). Furthermore recruitment to these trials predate by 7 years and more the current problems with HCAI. Although recent European guidelines recommend Fluoroquinolone prophylaxis in severe neutropenia, adherence to this is not universal (Meunier 2008). In trials where resistance data have been reported, patients on Fluoroquinolones did not develop more infections with pathogens resistant to the drug than patients on placebo (relative risk, 1.04 [95%CI, 0.73-1.5]). By reducing the number of clinical infections levofloxacin may reduce the total amount of antibiotics used in these patients (Bucaneve et al, 2005) and lessen the emergence of resistance. While emergence of bacteria resistant to Fluoroquinolones can occur in units using Fluoroquinolone antibiotic prophylaxis, there are not clear data as to whether patients are harmed as a result (Baum et al 2000; Razonable et al 2002).

In summary, the above data show that Fluoroquinolone prophylaxis in neutropenia is very effective but there are concerns about inducing Fluoroquinolone resistant organisms and healthcare associated infections. This supports the equipoise position for this trial. No substantial trial of antibiotic prophylaxis in myeloma has been done. The proven efficacy of levofloxacin in neutropenic patients and the sensitivity to levofloxacin of bacteria that cause infection in myeloma indicate that levofloxacin prophylaxis will also be effective in myeloma. The higher absolute risk of early death in myeloma (~10% in the first 12 weeks from diagnosis in some risk groups) suggests that antibiotic prophylaxis may be even more effective in myeloma than in neutropenia. Since there is a need for such an antibiotic trial in myeloma, it provides an excellent opportunity to collect data on HCAI and quantify absolute risk of colonisation and infection during antibiotic prophylaxis. Data from our proposed trial will help inform rational decisions about risks and benefits of antibiotic prophylaxis in many areas of medicine.

3. Trial Objective

To assess the risks, benefits and cost effectiveness of levofloxacin in newly diagnosed symptomatic myeloma by a prospective, multi-centre, randomised, double-blind, placebo-controlled trial.

4. Trial Hypothesis

Levofloxacin used once daily as anti-bacterial prophylaxis in newly diagnosed symptomatic myeloma will:-

1) Reduce the rate of febrile episodes, hospitalisation, and death
2) Increase response to anti-myeloma therapy
3) Improve quality of life and overall survival

The trial will also test if levofloxacin affects the carriage of and invasive infection by three important groups of bacteria; *C. difficile, S. aureus* (including MRSA) and ESBL coliforms.

1) Is the carriage of these organisms increased in patients receiving levofloxacin compared to those receiving placebo?

2) Is the carriage of these organisms associated with later invasive infections?
3) Does levofloxacin increase the rate of invasive infections by these three groups of organisms?

5. Trial Design

TEAMM is a randomized, double-blind, placebo-controlled multi-centre phase III trial assessing the benefit of antibiotic prophylaxis and its effect on health care associated infections.

All patients will receive anti-myeloma therapy

Experimental arm: Levofloxacin 500mg once daily orally for 12 weeks

Control arm: Placebo once daily orally for 12 weeks

Treatment allocation will be 1:1

6. Outcome Measures

6.1 Primary outcome from randomisation to 12 weeks

- Number of febrile episodes in the first 12 weeks from randomisation. A febrile episode is identified and counted by:
    - A single oral temperature ≥38° C (recorded **EITHER** by a health care professional **OR** by the patient/carer provided that the patient/carer has been trained and assessed as competent in temperature taking) **AND** that the patient is then given antibiotics
    - A single febrile episode is defined as the initial febrile event and any subsequent fevers until that course of antibiotics have been stopped
    - Capture of Febrile episodes will be via 1) documentation in hospital and 2) via patient diary cards. Patient diary cards will form part of the CRF returned four weekly.

6.2 Secondary outcomes from randomisation to 12 weeks

- Number of deaths and infection related deaths
- Number of days in hospital
- Number of days in hospital on antibiotics
- Carriage and invasive infections with *S. aureus, C. difficile* and ESBL coliforms
- Patient characteristics, steroid usage and indices of immunocompetence and their relation to colonisation by and development of infection from *S. aureus, C. difficile* and ESBL coliforms and non-HCAI and ECOG performance status
- Number of clinically documented total infections, episodes of severe sepsis (CTCAE grade 3 or 4) and suspected infections
- Incidence of microbiologically proven infections, the pathogens and their susceptibility to antibiotics
- Days on antibiotic therapy for treatment of infection
- Response to anti-myeloma therapy and its relationship to infection

6.3 Secondary outcomes from randomisation to beyond 12 weeks

- Carriage and invasive infections with *S. aureus, C. difficile* and ESBL coliforms between 12 and 16 weeks to assess for delayed affects from the intervention that is stopped at 12 weeks
- Response to anti-myeloma therapy at 16 weeks. Because of the half life of paraproteins measurement of myeloma response cannot be undertaken until a minimum of 4 weeks after an intervention
- Quality of life (4 weekly questionnaires up to 16 weeks)
- Health economics (daily diary card which captures elements of health resource use in combination with information captured on the CRF)
- Overall survival

7. Patient Selection & Eligibility

7.1 Inclusion Criteria

Patients with the following characteristics are eligible for this trial:

- Age ≥ 21 years and able to give informed consent
- Patient with newly diagnosed symptomatic myeloma based on internationally agreed criteria (see appendix 1 for diagnostic criteria).
- Patient that is no more than 7 days into starting a programme of anti-myeloma therapy or within 14 days into starting anti-myeloma therapy if already on a broad spectrum antibacterial agent. (Patients are eligible to be randomised prior to commencement of anti-myeloma therapy if they have an anticipated start date and that the trial drug is commenced within the 7 days prior or 7 days after commencing their anti-myeloma therapy).
- Provision of written informed consent

7.2 Exclusion Criteria

Patients with the following characteristics are ineligible for this trial:

- Patients with contraindication to Levofloxacin:-
  - known to have sensitivity / allergy to Levofloxacin or other quinolones
  - Patients with a history of tendon disorders related to fluoroquinolone administration
  - Patients receiving other prophylactic antibiotic treatment (excluding pneumocystis prophylaxis if regarded as essential)
  - Patients receiving amiodarone or arsenic trioxide
  - Patients on active antiepileptic treatment
- Women of childbearing age who are not willing to use appropriate methods of contraception to prevent pregnancy or women that are breastfeeding
- Patient thought to have mandatory requirement for prophylactic antibiotics
- Patient who is not going to receive anti myeloma therapy (see section 7.3)

7.3 Eligible chemotherapy regimens and accepted supportive practices

- All forms of anti-myeloma therapy excluding the use of supportive therapies *alone*. Eg Bisphosphonates alone, Erythropoietin or transfusions alone without anti-myeloma therapy added. (ie the patient must be on an anti-myeloma therapy. Dexamethasone is allowed as an anti-myeloma therapy).
- Supportive therapy practices common to a centre/unit are allowed, including the use of prophylactic antivirals and prophylactic pneumocystis therapy, if felt indicated.

7.4 Number of patients

A total of 800 patients will be required. The aim is to complete accrual within 4 years.

8. Randomisation Procedure

Written informed consent for entry into the trial must be obtained prior to randomisation and treatment allocation will be 1:1.

Randomisation will be via the telephone. A minimisation strategy will be used to randomise patients using a computer to generate a trial number and a drug pack number for each patient.

Warwick Clinical Trials Unit	**Tel: 02476 150402 (Mon-Fri, 9am to 5pm)** **Fax: 02476 151586**

9. Treatment Plan

9.1 Study Treatment

All patients will receive anti-myeloma therapy and supportive care including bisphosphonates as per standard practice. If it is intended that the patient will proceed to High Dose Therapy with Stem Cell Return, this information will be collected at randomisation and taken into account during stratification.

Within 7 days of starting a programme of anti-myeloma therapy (or within 14 days of starting anti-myeloma therapy if already on a broad spectrum antibacterial agent) patients will receive two 250mg Levofloxacin or placebo tablets daily for 12 weeks from trial entry.

Estimated Glomerular Filtration Rate (eGFR) as calculated by the MDRD formula should be assessed prior to commencement of treatment and reassessed at a minimum of 4 weekly' to identify changes in renal function that would necessitate a change in dose of levofloxacin *(see appendix 5 for the formula and a link to an online calculator).*

People with estimated glomerular filtration >50 ml/min will take 2 tablets daily (dose of 500mg)

People with estimated glomerular filtration 20 - 50 ml/min will take 1 tablet daily (dose of 250mg)

People with estimated glomerular filtration <20 ml/min will take ½ a tablet daily (dose of 125 mg)

Both the active tablets and the placebo tablets are in an identical breakable tablet form. Dose reduction can be achieved by breaking the tablets in half. Tablet cutters can be supplied if required.

In the event of a febrile episode it is suggested that patients remain on study drug and management of infection will be as for an individual who has been taking levofloxacin 500mg daily. Patients will be treated as per standard practice according to the nature of the infection. On resolution of infection the patient will continue taking the trial drug. If a patient has stopped the study drug whilst being treated for an infection this must be restarted promptly upon resolution. Only in a circumstance that the physician in charge considers it necessary for patient management will the trial drugs be unblinded; see section 11.3 for details.

9.2 Special warnings or possible drug interactions

There are a number of special warnings or possible drug interactions where Levofloxacin should be used with caution. The table below details these:

Table 1. Special warnings or possible drug interactions for Levofloxacin

Conditions that predispose to seizures	Risk of exacerbation
Tendinitis and tendon rupture	Study drug must be stopped if either occurs
Exposure to excessive sunlight	Discontinue if photosensitivity occurs
Myasthenia Gravis	Risk of exacerbation
G6PD deficiency	Risk of exacerbation
NSAIDs	May lower cerebral seizure threshold. Use with caution.
Drugs known to prolong QT interval *(e.g. Class 1A and III antiarrhhythmics, tricyclic antidepressants & Macrolides)*	Use with caution
Warfarin	Increased risk of high INR and/or bleeding. INR should be monitored soon after starting study drug.

	Patients on Warfarin are asked to ensure that the anticoagulant clinic is informed within 2 to 5 days of starting the study drug (or within 2 to 5 days from hospital discharge). (But patients need to inform anticoagulant clinic of new anti-myeloma therapy and possible Warfarin interaction anyhow).
Iron, magnesium and aluminium containing antacids	Should not be taken for 2 hours either side of Levofloxacin

9.3 Study Drug: Supply, dispensing and accountability

MODEPHARMA will organise the supply of labelled treatment boxes containing either Levofloxacin or placebo-to-match. At the start of the trial, each patient will be supplied with 1 patient pack which will contain enough trial tablets to cover the whole 12 week period. Each patient pack will contain 6 blister strips and each blister strip will contain 28 tablets.
Each of the blisters and each of the cartons will bear a unique randomisation number and the randomisation system will allocate a carton to a patient. Drugs will be supplied to the pharmacy in numbered packs and the tablets and packaging will be indistinguishable by either the patient or their clinicians. The active Levofloxacin and placebo tablets will be manufactured and QP released for clinical trial use by Pharmathen. If further drug packs are required, requests can be made to the trial coordinator who will order more drug packs from MODEPHARMA.

Logistics of sending trial drugs / placebo to hospital pharmacies will be monitored by the trial co-ordinator using study logs. When drugs are dispensed from pharmacy or returned, records should be maintained on a drug accountability log.

Unused/ returned or expired drugs will be disposed of by the hospital pharmacies. However the coordinating centre must be informed first.

9.4 Supportive Therapy

Supportive therapy practices common to a centre/unit are allowed, including the use of prophylactic antivirals and prophylactic pneumocystis therapy, if felt essential. Other prophylactic antibacterial antibiotics are not allowed.

9.5 Concomitant illness and medication

Details of any concomitant illness (any illness present at the start of the trial) should be recorded at trial entry. Details of any concomitant medication (any medication, other than the trial product, that is taken during the trial and during screening) should be recorded at trial entry. Any changes in concomitant medication should be recorded at each visit. If the change influences the subject's eligibility to continue in the trial, the investigator must be informed.

10. Laboratory Investigations & Data Collection

10.1 Local Laboratory Investigations

We will request results for the following investigations that are recommended by national and international guidelines for the routine clinical diagnosis of myeloma, and to provide a baseline for the clinical care of patients on a day-to-day basis:

- FBC+ESR/viscosity, urea and electrolytes, creatinine, calcium, albumin, serum protein and urine electrophoresis, serum and urine paraprotein typing and quantitation, immunoglobulins, β2 microglobulin, +/- serum free light chains.

- An axial skeletal survey. Axial skeletal survey may have been supplemented by CT and/or MRI investigation when appropriate
- Bone marrow aspirate +/- trephine.

At each follow-up visit, the following investigations are done, in line with standard clinical care:

- FBC, urea and electrolytes, creatinine, calcium, immunoglobulins, serum +/- urine paraprotein quantitation, +/- serum free light chain
- Clinical and performance status assessment including weight

10.2 Central Trial Team Laboratory Investigations

The following samples are required for analysis by the central trial laboratories using request forms, sample bottles and packaging as provided by the trial team:

Microbiology → St Georges

Department Medical Microbiology, St Georges Hospital, Blackshaw Road, Tooting, London, SW17 0RE
Tel: 020 8725 2683/5694, Fax: 020 8725 5694

Immunology Samples → Birmingham

Clinical Immunology Service, Medical School, University of Birmingham, PO Box 1894, Edgbaston, Birmingham, B15 2TT
Tel: 0121 414 4069, Fax: 0121 414 3069

10.2.1 Microbiology

A Stool sample and a nasal swab need to be taken before commencement of study drug, and at 4-weekly intervals up to and including 16 weeks. These will be used to assess carriage of *S. aureus, C. difficile* and ESBL coliforms.

Microbiology samples (stool sample and nasal swab) need to be posted to St Georges using the details above and the *TEAMM* Microbiology sample request form. Packs with instructions for despatching samples will be provided in advance.

These will be cultured for *C. difficile* and toxogenic strains identified. Strains will be further identified by ribotyping. Extended MLVA typing will be performed on all isolates in Birmingham (PMH lab). ESBL positive Gram negative bacteria from faecal screens and clinical specimens (when available) will be identified and sent to Birmingham (PMH lab) for genotyping of CTX-M betalactamase genes using dHPLC. Nose swabs will be cultured for MRSA and isolates typed and stored. All samples will be anonymised to the microbiology laboratory and no results will be directly reported to clinicians. The normal standard of care with screening for MRSA and diagnosis of *C. difficile* and other infections will remain unchanged during the study.

If patients are admitted as an infection related SAE (including deaths) routine samples will be taken for local microbiological diagnosis. In this event the PI at the site will identify this as an SAE and this SAE will be notified to the central microbiology laboratory and the central lab can then liaise with the local laboratory about the transfer of any isolates.

10.2.2 Immunology

An assessment of paraprotein levels, prognostic factors and immunocompetence will be made prior to randomisation and at 4 weekly intervals up to and including 16 weeks after commencement of treatment on the study drug.

Samples to send to Birmingham at entry to trial:

- Blood clotted 12-20mls (2x red topped tubes)
- Blood EDTA 8mls (2x purple topped tubes)
- Random urine Sample 20mls (Universal containers supplied)

Samples to send to Birmingham at 4, 8, 12 & 16 weeks

- Blood clotted 12-20mls (2x red topped tubes)
- Blood EDTA 4mls (1x purple topped tubes)
- Random urine sample 20mls (Universal supplied)

Measurements at entry and at 8 and 12 weeks will include levels of:

- Whole and flc paraprotein in serum and urine
- Beta-2 microglobulin, albumin, creatinine, calcium, CRP
- Complement components C3 & C4, MBL
- Acute phase response proteins and cytokines
- Serum levels of polyclonal immunoglobulin. Specific antibody against panels of both bacterial and viral antigenic targets and type I natural antibody levels.
- Single platform flowcytometric enumeration of lymphocyte subsets including type I and type 2 B cells, memory B cells; gamma/delta, CD4 & CD8 T cells; naive and memory subsets; Treg cells; NK cells
- Monocyte subsets defined by SD14 and CD16; dendritic cells
- At entry and 12 weeks buffy coat cells, plasma and serum will be alliquoted and stored at -80°c

Measurements at 4 and 16 weeks will include levels of:

- Whole and flc paraprotein in serum and urine
- Beta-2 microglobulin, albumin, creatinine, calcium, CRP response, markers of inflammation and humoral and cellular immunocompetence.

10.3 Non- Laboratory Assessments and data collection

Completed data forms should be returned to:

TEAMM Trial Office
Warwick Clinical Trials Unit
University of Warwick
Gibbet Hill Campus
CV4 7AL

10.3.1 Assessment of Febrile Episodes and compliance

Patient diaries will be issued to patients with their study drug and they will be shown how to fill them out daily. Patients will be given digital oral thermometers, instructed how to use them and asked to self report their oral temperature daily. It is suggested this is done at the time they take their tablet and at any other time if they feel hot or unwell. It is also suggested that patients routinely take their tablet at a similar time each day. Compliance will be monitored at least 4 weekly by reviewing patients empty blister packs and daily diary cards. Sites will request that patients return all used and unused blister packs each time they return, along with their patient diaries.

The data collected by patients on their diary cards will be transcribed at 4 weekly clinic visits onto CRFs. Both the diary and the CRF should be sent to the coordinating centre at Warwick.

10.3.2 Quality of Life & Health Resource Use Assessment

The first set of Quality of life forms should be given to patients after written consent is obtained but prior to randomisation. Further quality of life forms will need to be administered at 4 weeks, 8 weeks, 12 weeks and 16 weeks post commencement of study drug. An assessment of Health Economics will be via questions on

the daily diary card and data collected via the CRF. Health resource use questions will be included in the diary card during treatment and a separate post treatment diary will be given for the four weeks following treatment in order to capture this information up to 16 weeks.

10.3.3 Schedule of delivery of intervention and data collection

Patients will receive levofloxacin or placebo for 12 weeks from trial entry. Patients will be fully assessed as described below at entry to the trial, 4 weeks, 8 weeks, 12, weeks and 16 weeks. These detailed assessments will include patient diary, clinical review and central laboratory assessment for immunology and microbiology.

10.3.1 Follow-up

After the initial 16 weeks patients will be followed up as per their standard myeloma care. Patients in the trial will be followed up with an appointment at 12 months post randomisation. At the appointment there will be a clinical review of the patient and blood samples will be taken for central laboratory assessment. After this 12 month period, active follow-up will stop and we will request simple information regarding the patient's disease status on an annual basis only. Long term follow-up will also continue passively by flagging cases with ONS.

Table 2. Schedule of Delivery

		Follow-up visit				
	Start of Study Treatment	**4 weeks**	**8 weeks**	**12 weeks** (End of treatment)	**16 weeks**	**12 months**
Informed consent taken	x					
Medical history to include ECOG performance status and weight and co-morbidities	x	x	x	x	x	x
Inclusion criteria satisfied	x					
Levofloxacin/placebo supplied to patient	x					
Quality of Life (EQ-5D, EORTC-QLQ C30 & HADS)	x	x	x	x	x	
Patient diary supplied to patient (includes questions on health resource use)	x	x	x			
Post Treatment Patient diary supplied to patient				x		
Compliance with trial medication assessed (counting of empty blister packs)		x	x	x		
Details of febrile episodes infections and admissions collected	x	x	x	x	x	x
Adverse events		x	x	x	x	
Details of supportive care collected	x	x	x	x	x	x
12-20 ml clotted peripheral blood, 8mls EDTA blood(at start of treatment) 4mls EDTA blood thereafter, 20mls urine to Birmingham	x	x	x	x	x	x
Stool sample and nasal swab to St Georges	x	x	x	x	x	
Bone marrow aspirate +/- trephine	x					
Full blood count	x	x	x	x	x	x
Biochemistry screen	x	x	x	x	x	x
eGFR using MDRD formula	x	x	x	x	x	x

11. Safety & Adverse Event Management

11.1 Definitions

11.1.1 Adverse Events (AE)

An adverse event is defined as any untoward medical occurrence in a subject *(administered a medicinal product)* and which does not necessarily have a causal relationship with this treatment.

11.1.2 Adverse reactions (AR)

An adverse reaction is defined as any untoward and unintended response to the study drug (levofloxacin). A causal relationship between the trial treatment and an adverse event is at least a reasonable possibility, ie the relationship cannot be ruled out.

11.1.3 Serious Adverse Events (SAEs)

A serious adverse event is an AE that fulfils one or more of the following criteria:

- Results in death
- Is immediately life-threatening
- Requires hospitalisation or prolongation of existing hospitalisation
- Development of any grade 4 non-haematological toxicity (excluding alopecia)
- Results in persistent or significant disability or incapacity
- Is otherwise medically significant (e.g. important medical events that may not be immediately life-threatening or result in death or hospitalisation but may jeopardise the patient or may require intervention to prevent one of the other outcomes listed above, excluding new cancers or result of overdose)

11.1.4 Serious Adverse Reactions (SARs)

A SAR is defined as an SAE that has a definite, probable or possible causal relationship to the study drug (levofloxacin). A list of expected SARs are provided in ***Table 3***. The causality of SAEs (i.e., relationship to levofloxacin) will be assessed by the investigator(s) on the SAE form.

11.1.5 Suspected Unexpected Serious Adverse Reactions (SUSARs)

Suspected Unexpected Serious Adverse Reactions (SUSARs) are SARs that are also unexpected i.e. their nature or severity is not consistent with the Summary of Product Characteristics and are considered to be caused by the trial drug.

11.2 Reporting Procedures

11.2.1 Terminology and severity

An adverse event term must be provided for each adverse event, preferably using the Short Name as listed in the Common Terminology Criteria for Adverse Events v4.03 (CTCAE). Severity of each adverse event 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

There is also a table of grading for common infections in appendix 6.

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 4 = Life threatening 5 = Fatal

11.2.2 Causality

The PI or other delegated site investigators must perform an evaluation of causality for each adverse event.

Causal relationship to the trial treatment must be determined as follows:

• **None** - There is no evidence of any causal relationship.

• **Unlikely** - There is little evidence to suggest a causal relationship (e.g. because the event did not occur within a reasonable time after administration of the trial treatment). There is another reasonable explanation of the event (e.g. the patient's clinical condition, other concomitant medications).

• **Possible** - There is some evidence to suggest a causal relationship (e.g. because the event occurs within a reasonable time after administration of the trial treatment). However, the influence of other factors may have contributed to the event (e.g. the patient's clinical condition, other concomitant medications).

• **Probable** - There is evidence to suggest a causal relationship and the influence of other factors is unlikely.

• **Definitely** - There is clear evidence to suggest a causal relationship and other possible contributing factors can be ruled out.

11.2.3 Reporting ARs

All Adverse Reactions that occur between the first administration of study drug and 30 days post last dose of study drug must be recorded in the trial CRFs, together with data including date of onset and resolution, outcome, severity and causality for the trial drug.

See Table 5 for expected ARs.

11.2.4 Reporting SAEs, SAR's and SUSARs

Events that DO NOT require reporting as an SAE

The following events **do not** require reporting as an SAE for this trial, but must be recorded in the relevant section(s) of the CRF:

Table 3. Expected SAEs that relate to myeloma and its treatment that do not need reporting (except in the CRF)

Disease progression
Disease related deaths
Routine treatment or monitoring of the studied indication not associated with any deterioration in condition
Treatment, which was elective or pre-planned, for a pre-existing condition, not associated with any deterioration in condition
General care, not associated with any deterioration in condition
Treatment on an emergency outpatient basis for an event not fulfilling any of the definitions of serious given above (see 14.1.3) and not resulting in hospital admission
Hospitalisation for palliative care
Grade 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 14.1.3)
Treatment (including hospitalisation, or extension of hospitalisation) for transfusions or pain relief
Surgical interventions for skeletal related events ,e.g. fixation of fractures, vertebroplasty
Skeletal related events including bone fractures, spinal cord compression, increased bone pain
Hypercalcaemia
Extravasation
Patients may present with some pre-existing toxicities which meet the criteria set in 14.1.3, but it is only the development of these toxicities after entering the trial which should be reported

Expected SAEs that DO require reporting as SAEs

The events in table 4 and 5 will be classed as expected SAEs within this trial and therefore will not be reportable as SUSARs. These should be reviewed and classed by a clinically qualified person.

***Table 4. Expected SAEs* related to myeloma and its treatment (that nevertheless require reporting as SAEs)**

Infections, including neutropenic fever
Bowel disturbance
Venous thromboembolic events
Renal failure

Table 5. Expected SARs related to levofloxacin as stated in the levofloxacin SmPC

Common	Diarrhoea, nausea, Increased hepatic enzymes (ALT/AST, alkaline phosphatise, GGT)
Uncommon	Fungal infection, leukopenia, eosinophilia, anorexia, insomnia, nervousness, dizziness, headache, somnolence, vertigo, vomiting, abdominal pain, dyspepsia, flatulence, constipation, increase in blood bilirubin, rash, pruritus, increased blood creatinine, asthenia
Rare	Thrombocytopenia, neutropenia, psychotic disorder, depression, confusional state, agitation, anxiety, convulsion, tremor, paraesthesia, tachycardia, hypotension, bronchospasm, dyspnoea, haemorrhagic diarrhoea, urticaria, tendon disorder
Very rare	Agranulocytosis, anaphylactic shock, hypoglycaemia, suicidal ideation/hallucination, peripheral neuropathy, taste distubance, visual disturbance, hearing disturbance, allergic pneumonitis, hepatitis, angioneurotic oedema, photosensitivity, tendon rupture, acute renal failure, pyrexia.

The most recent and relevant Summary of Product Characteristics must be referred to for more specific details and potential drug interactions.

All SAEs or SUSARs that occur between trial entry and 30 days after the end of the trial drug/intervention will be reported.

SAEs and SUSARs will be reported using the SAE form in the patient's CRF. The Principal Investigator in each centre must report any SAEs and SUSARs to the Trial Co-ordinating Centre within 24 hours of them becoming aware of it.

The SAE form should be completed and faxed to Warwick Clinical Trials Unit on **02476 150549**. The trial co-ordinator will liaise with the Investigator to compile all the necessary information. The Trial Co-ordinating Centre is responsible for reporting adverse events to the sponsor, ethics committee and MHRA within required timelines.

11.3 Blinding & Unblinding

11.3.1 Methods for ensuring blinding

The levofloxacin and placebo tablets will be packaged in coded but otherwise identical blister packs. Neither the patient nor the clinical team responsible for the patients care will know how to break the treatment code. The treatment code can only be broken by the Emergency Scientific and Medical Services (eSMS) team at Guy's and St Thomas' Hospital.

11.3.2 Methods for unblinding the study

Emergency unblinding may be requested on grounds of safety by any clinician involved in the medical care of the patient. Emergency unblinding will be performed by telephone contact with the Emergency Scientific and Medical Services (eSMS) team at Guy's and St Thomas' Hospital. The phones will be manned **24 hours a day, 365 days a year.** This option may be used ONLY if the patient's future treatment requires knowledge of the treatment assignment and there will be very few situations where unblinding will be necessary. In the event of invasive clostridium difficile infection the trial tablets should be discontinued and later unblinded if felt necessary for the safety of the patient. In the event of a suspected allergic reaction to the trial tablets, the trial tablets should be discontinued and unblinded if felt necessary for the safety of the patient.

Emergency Scientific and Medical Services (eSMS)
0207 188 0300

11.3.3 Procedures in case of overdose

According to toxicity studies in animals or clinical pharmacology studies performed with supra-therapeutic doses, the most important signs to be expected following acute overdosage of Levofloxacin tablets are central nervous system symptoms such as confusion, dizziness, impairment of consciousness, and convulsive seizures, increases in QT interval as well as gastro-intestinal reactions such as nausea and mucosal erosions.

In the event of overdose, symptomatic treatment should be implemented. ECG monitoring should be undertaken, because of the possibility of QT interval prolongation. Antacids may be used for protection of gastric mucosa. Haemodialysis, including peritoneal dialysis and CAPD, are not effective in removing levofloxacin from the body. No specific antidote exists.

11.4 Procedures in case of pregnancy

Pregnancy itself is not regarded as an adverse event unless there is a suspicion that the investigational product under study may have interfered with the effectiveness of a contraceptive medication or if as is likely, the anti-myeloma therapy is contraindicated in pregnancy. However, the outcome of all pregnancies (spontaneous miscarriage, elective termination, normal birth or congenital abnormality) must be followed up and documented even if the subject was discontinued from the study.

All reports of congenital abnormalities/birth defects must be reported and followed up as a SAE.

12. Post Randomisation Withdrawals & Exclusions

- Subjects may be discontinued from the trial treatment and/or the trial at any time without prejudice. Unless a subject explicitly withdraws their consent, they should be followed-up wherever possible and data collected as per the protocol until the end of the trial.
- Subjects may be withdrawn from the trial at the discretion of the Investigator and/or Trials Steering Committee due to safety concerns.

13. Statistical Considerations

13.1 Stratification

Randomisation procedures are currently being designed in conjunction with the trial team and the trial statisticians. The similarity across treatment arms will be maintained through stratification. The stratification criteria are as follows:

- Centre
- Intention to give high dose chemotherapy with stem cell rescue
- Renal failure as measured by Estimated Glomerular Filtration Rate (eGFR).

13.2 Power and sample size

The primary and first set of secondary outcomes will be reached within 12 weeks of entry.

The primary outcome measure is time to first febrile episode or death from all causes, using a Kaplan-Meier survival curve. Assuming the proportion of patients having a febrile episode or death is 30% in the first 3 months and prophylactic antibiotics would reduce that rate to 20%, then recruiting 800 patients into the trial (400 in each arm) would allow differences in excess of 10% to be detected with a 90% power using a 2-sided test at the 5% level of significance.

800 patients will also allow detection of a levofloxacin induced 3 fold increase in the rate of *C. difficile* positive stools (from 5% to 15%, MRSA and ESBL coliform carriage from entry to the trial to 12 weeks, with a 95% power and a 5% level of significance (2-sided test).

Other analyses include incidence of probable infections with site, severity and therapy; response to anti-myeloma therapy and its relationship to infection; patient characteristics and indices of immunocompetence (blood leukocyte subset enumeration and antibacterial antibody titres) as prognostic markers for colonization and invasive infection by antibiotic resistant organisms; health economics and quality of life) by daily diary card, 4 weekly EQ5D up to 16 weeks). With 800 patients we will be able to report reliable estimates for these secondary outcomes.

13.3 Analysis plan

The main analysis comparing time to first febrile episode or death from all causes, will be carried out using a log-rank comparison with the start time being the date of randomization and the event being the date of febrile episode, or censored at the time of death or withdrawal for those not having a febrile episode.

The secondary endpoints such as clostridium difficile stools, MRSA and ESBL coliform carriage rates and number of invasive infections associated with the identical organism previously carried will be assessed using chi-squared tests with continuity adjustments. Mantel-Haenszel tests for combining two-by-two tables will then be used to adjust for stratification variables and various prognostic factors. Patients who are randomized and started treatment will be included in the analyses. Sensitivity analyses will be carried out assessing the impact of those patients randomized but who did not start treatment and those who did not comply or dropped-out.

Overall survival will be calculated from the date of randomization to the date of death or date of censor as appropriate. Overall survival will be carried out on all cause mortality and assessed using Kaplan-Meier curves. The main treatment effect will be assessed using the log- rank test. The analyses of all other secondary endpoints, incidence of probable infections with site, severity and therapy, response to anti-myeloma therapy and its relationship to infection and indices of immunocompetence (blood leukocyte subset enumeration and anti-bacterial antibody titres) will be undertaken using the appropriate statistical analyses tools.

13.4 Independent Data & Safety Monitoring Committee (DSMC)

An independent data and safety monitoring committee will be established for this trial, consisting of an independent statistician, haematologist and microbiologist. Their main objective will be to advise the trial steering committee as to whether there is evidence or reason why the study should be amended or terminated based on recruitment rates, compliance, safety or efficacy. The DSMC will meet after the first 50 patients have been recruited and annually thereafter. Confidential reports containing recruitment, protocol compliance, safety data and interim analyses of outcomes (not formally tested outside of the trial statistical analyses plan, to be agreed with the DSMC) will be reviewed by the DSMC. Interim analyses of the primary outcome will be presented to the DSMC using conservative tests with significance determine by a p-value of 0.001 (to preserve the overall alpha level of 0.05).

13.5 Trial timetable and milestones

The project has already been through an intensive design phase, engagement of a team of experts and consumers. The study will start in **September 2011** and the first 18 months will involve setting up the trial at each centre (anticipated 110 centres though the existing myeloma trials network) and completion of all

ethics and local R&D approval. Recruitment phase will be 4 years with an additional 6 months for data gathering and analyses. Funding is requested for flagging with ONS for additional follow up and death certificates. Anticipating a positive outcome for this exciting trial proposal, the TEAMM investigators will carry out as much preparation as possible prior to the full proposal being considered. Members of the team are experienced cancer clinical trialists, with a successful track record in design, running and analysis of multi-centre randomised trials.

This study will have no competing studies on the NCRI haematology cancer portfolio. The study itself maps out onto standard clinical practice and thus centres will not find it difficult to participate. We have factored a 10% non-compliance and drop-out rate. Details of all patients approached to participate but who refuse will be documented along with reason for refusal via screening logs.

Oct 2010 – Aug 2011:	Recruitment of trial team
	Finalisation of Trial Protocol
	Gain relevant approvals
	Preparation of trial documentation
Sep 2011:	**Grant starts**
Dec 2011:	First centre open; First patient recruited
Feb 2012:	Trial Launch meeting
Apr 2012:	17 centres open, 25 patients recruited
Jun 2012:	1st Data & Safety Monitoring Committee meeting
	Trial Steering Committee meeting and review
Dec 2012:	50 centres open, 80 patients recruited
Jul 2013:	2nd Data & Safety Monitoring Committee meeting
	Trial Steering Committee meeting and review
Dec 2013:	80 centres open, 240 patients recruited
Jul 2014:	3rd Data & Safety Monitoring Committee meeting
	Trial Steering Committee meeting and review
Dec 2014:	110 centres open, 480 patients recruited
Jul 2015:	4th Data & Safety Monitoring Committee meeting
	Trial Steering Committee meeting and review
Dec 2015:	**Recruitment of 800 patients complete**
May 2016:	Start of analyses of trial results
Jul 2016:	Final Data and Safety Monitoring Committee to review trial results
	Steering Committee meeting and review trial results
Sep 2016:	**Final report to HTA and preparation of manuscript**

14. Economic Evaluation

Economic evaluation will be carried out by a health economics senior research fellow at Leeds under the guidance of Claire Hulme. The methods will, as far as possible, adhere with the recommendations of the NICE Reference Case (NICE 2008). The economic evaluation will consist of a within-trial analysis and economic simulation.

Within trial analysis will compare direct costs and 16 week outcomes of patients randomized to levofloxacin versus placebo. The perspective adopted will be that of the NHS and Public Social Services. A costing study will record chemotherapy and other resource use (e.g. drugs, number of days in hospital, outpatient visits, laboratory/ radiological tests, GP & community nurse visits, social care service provision etc). Resource utilisation will be captured from hospital systems and using a patient diary. The design of the patient diary will build upon the work of Goosens et al (JClinEpi 2002). Unit costs for health and social care resources will be derived from local and national sources and performed in line with best practice.[Graves 2002] Costs will be standardised to current prices where possible using the NHS Pay and Prices Index produced by PSSRU (Curtis et al 2010). Because of the short follow up period, we will not discount costs or benefits.

Data will be collected at baseline, 4, 8, 12, and 16 weeks to estimate incremental cost-effectiveness ratios (ICERs) comparing the intervention with the control group in terms of the primary outcome measure (febrile episodes) and costs (Drummond et al 2005). Mortality and quality of life (EQ-5D see appendix 7) over the study period will be used to generate quality-adjusted life-years (QALYs).[Richardson & Manca 2004] Parameter uncertainty will be quantified using non-parametric bootstrapping techniques. Outputs will be presented as ICERs, cost effectiveness acceptability curves and expected net benefit. As well as identifying the most cost-effective means of achieving a QALY, the NICE threshold of £20,000 per QALY will be applied when considering prophylaxis (NICE 2008). The impact of missing data will be examined using imputation methods. Sensitivity analyses will consider key cost drivers and factors that might affect the outcomes measured in order to explore uncertainty in the conclusions drawn (Glick et al).

The within trial analysis will only address colonisation and infection in trial patients (direct impact). Any indirect impact of resistant microorganisms on the ward or unit in which prophylaxis is adopted (potentially harming other patients) or impact of longer-term changes in resistance to levofloxacin in the population at large will not be included. If differences in levels of resistance (e.g. MRSA) or infections (e.g. C. *difficile*) are observed between the trial arms, the economic consequences of these will be addressed using a system dynamics approach. This form of simulation has proved to be a useful analysis tool to evaluate the broader impact of clinical interventions, including in areas such as infections and antibiotic resistance.[Higgins 2002; Homer 2000; Dangerfield 2001; Fone 2003] In the UK, the NHS Institute for Innovation & Improvement has recently advocated use of simulation to assess the impact of change across a whole system.[Gaunt 2008].

15. Data Management & Patient Confidentiality

15.1 Data Acquisition

Personal data collected during the trial will be handled and stored in accordance with the 1998 Data Protection Act. The Case Report Forms (CRFs) will be designed by the Trial Co-ordinator in conjunction with the Chief Investigator and Statistician. Original copies should be sent to the coordinating team at Warwick and copies are stored in the patient notes on site. On receipt, all forms will be checked for completeness and congruity. Forms containing empty data fields or data anomalies will be queried and returned to site for resolution.

15.2 Confidentiality

The personal data recorded on all documents will be regarded as strictly confidential. To preserve the patient's anonymity, only their initials, date of birth, and hospital number will be recorded on the CRFs. With the patient's permission, their name will be collected at randomisation to allow flagging with the Office of National Statistics and to allow haematology sample tracking. Patients should be assured that their confidentiality will be respected at all times.

The investigator must maintain documents not for submission to the trials unit (e.g. patients' written consent forms) in strict confidence. In the case of special problems and/or governmental queries, it will be necessary to have access to the complete study records, provided that patient confidentiality is protected. Warwick Medical School Clinical Trials Unit will maintain the confidentiality of all patient data and will not disclose information by which patients may be identified to any third party, other than those directly involved in the treatment of the patient's Myeloma.

The database will be set up by the Programming Team at WCTU and all specifications (ie database variables, validation checks, screens) will be agreed between the programmer, statistician and trial co-ordinator.

15.3 Data storage & Archiving

All essential documentation and trial records will be stored by WCTU in conformance with the applicable regulatory requirements and access to stored information will be restricted to authorised personnel.

Trial documentation and data will be archived for at least five years after completion of the trial.

16. Study Organisation

16.1 Trial Management Group (TMG)

The Trial Management Group has considerable expertise in all aspects of design, running, quality assurance and analysis of the trial. A list of proposed members is as follows:

Lead Clinical Investigators: Mark Drayson, Stella Bowcock, Guy Pratt, Kwee Yong, Tim Planche, Peter Hawkey
Statisticians: Janet Dunn, Gulnaz Iqbal
Quality of Life advisors: Douglas Carroll, Anna Phillips
Health Economics advisor: Claire Hulme
Patient advocate lead: Eric Low

16.2 Trial Steering Committee (TSC)

The trial will be guided by a group of respected and experienced personnel and trialists as well as a 'lay' representative. The TSC will have an independent Chairperson. Face to face meetings will be held at regular intervals determined by need but not less than once a year. Routine business is conducted by email, post or teleconferencing.

The Steering Committee, in the development of this protocol and throughout the trial will take responsibility for:

- Major decisions such as a need to change the protocol for any reason
- Monitoring and supervising the progress of the trial
- Reviewing relevant information from other sources
- Considering recommendations from the DMEC
- Informing and advising on all aspects of the trial

An Independent Trials Steering Committee will be set-up with an independent chair, two other independent members and the lead investigators. Members of the TMG will be co-opted onto the TSC as appropriate.

16.3 Administration

The trial will be co-ordinated from Warwick Medical School Clinical Trials Unit, Warwick Medical School, and University of Warwick under the direction of Professor Janet Dunn. Clinical responsibility will be undertaken by the Lead Investigators of the Trial Management Group with specific expertise in Immunity and Infection, Microbiology and Hematology.

17. Patient Protection & Ethical Conduct

The trial will be conducted in full conformance with the principles of the Declaration of Helsinki and in accordance with UK legislation. The study will also adhere to the principles of ICH/ Good Clinical Practice (GCP). GCP-trained personnel will conduct the trial. Free GCP training will be given, through the local National Cancer Research Networks NCRN, to centres who do not have experience in conducting randomized, prospective, controlled, clinical trials.

Before enrolling patients into the trial, each trial site must ensure that the local conduct of the trial has the approval of the relevant trust Research & Development (R&D) department. Sites will not be permitted to enrol patients into the trial until written confirmation of R&D approval is received by Warwick Clinical Trials Unit.

The protocol, final version of the Patient Information Sheet and Consent Form and all written information given to trial subjects must be approved or given a favourable opinion in writing by an Ethics Committee as appropriate.

17.1 Indemnity

NHS indemnity covers NHS staff, medical academic staff with honorary contracts, and those conducting the trial. NHS bodies carry this risk themselves or spread it through the Clinical Negligence Scheme for Trusts, which provides unlimited cover for this risk.

The Universities of Birmingham and Warwick will indemnify the study in relation to the design and management of the research

18. Research Governance

18.1 Sponsor

The University of Birmingham and the University of Warwick will co-sponsor the *TEAMM* trial. The University of Warwick will act as the co-ordinating centre and will employ the trial coordinator and take responsibility for the day-to-day running of the trial, collecting & managing the data and pharmacovigilance.

18.2 Essential Documentation

A Trial Master file will be set up and held securely at the co-ordinating centre.

18.3 End of Trial

For the purposes of regulatory requirements, the end of trial is defined as the date of the last treatment visit for the last patient undergoing protocol treatment. The treatment phase will be followed by a non-interventional follow-up period which will continue until July 2016. For the purposes of Research Ethics Committee approval, the study end date is deemed to be the date of last data capture.

The trial will be stopped prematurely if:

- Mandated by the Ethics Committee
- Mandated by the Medicines and Healthcare products Regulatory Agency (MHRA)
- Following recommendations from the Data Monitoring and Ethics Committee (DMEC)
- Funding for the trial ceases

The Main Research Ethics Committee (MREC) and the MHRA will be notified in writing if the trial has been concluded or terminated early.

18.4 Financial Support

TEAMM has been funded by the National Institute for Health Research, Health Technology Programme.

HTA Project: 08/116/69 - Tackling Early Morbidity and Mortality in Myeloma: Assessing the benefit of antibiotic prophylaxis and its effect on healthcare associated infections

19. Dissemination & Publication

The results of the trial will be reported first to trial collaborators. The main report will be drafted by the trial co-ordinating team, and the final version will be agreed by the Steering Committee before submission for publication, on behalf of the collaboration.

The success of the trial depends on the collaboration of doctors, nurses and researchers from across the UK. 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).

20. References

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Appendix 1: Definition of Myeloma and related diseases

BCSH and UKMF Guidelines on the Management and Diagnosis of Multiple Myeloma Sept 2010

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

*If flow cytometry is performed, most plasma cells (>90%) will show a 'neoplastic' phenotype. Some patients may have no symptoms but have related organ or tissue impairment.

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

Appendix 2: ECOG performance status

Grade Description

0: Asymptomatic, fully active and able to carry out all pre-disease performance without restriction.

1: Symptomatic, fully ambulatory but restricted in physically strenuous activity and able to carry out performance of a light or sedentary nature e.g. light housework

2: Symptomatic, ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours: in bed less than 50% of the day

3: Symptomatic, capable of only limited self-care, confined to bed or chair more than 50% of waking hours, but not bed ridden

4: Completely disabled. Cannot undertake any self-care. Totally bed-ridden

Appendix 3: National Cancer Institute Common Toxicity Criteria (NCIC)

Toxicities will be assessed based on the National Cancer Institute Common Terminology Criteria for Adverse Events V4.0 (NCI-CTCAE). A copy is provided in the Investigator Site File and may be obtained at: http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_5x7.pdf

Published date: May 28, 2009

Appendix 4: International Myeloma Working Group uniform response criteria for multiple myeloma

Complete response* (CR)	Negative immunofixation of serum and urine and Disappearance of any soft tissue plasmacytomas, and <5% plasma cells in bone marrow
Stringent response (sCR)	CR as defined above plus Normal FLC ratio and Absence of clonal cells in bone marrow by immunohistochemistry or immunofluorescence
Very good partial response (VGPR)*	Serum and urine M-component detectable by immunofixation but not on electrophoresis or ≥90% or greater reduction in serum M-component plus urine M-component <100mg per 24 h
Partial response (PR)	≥50% reduction of serum M protein and reduction in 24-h urinary M protein by ≥90% or to <200mg per 24 h If the serum and urine M protein are unmeasurable, 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 unmeasurable, and serum free light assay is also unmeasurable, ≥50% reduction in bone marrow plasma cells is required in place of M protein, provided baseline percentage was ≥30% In addition to the above criteria, if present at baseline, ≥50% reduction in the size of soft tissue plasmacytomas is also required
Stable disease (SD)	Not meeting criteria for CR, VGPR, PR or progressive disease
Progressive disease (PD)*	Increase of 25% from lowest response value in any one or more of the following: Serum M-component (absolute increase must be ≥0.5 g/100 ml)** and/or Urine M-component (absolute increase must be ≥200mg per 24 h) and/or Only in patients without measurable serum and urine M-protein levels: the difference between involved and uninvolved FLC levels (absolute increase must be >100 mg/l) Bone marrow plasma cell percentage (absolute % must be ≥10%) 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 hypercalcemia (corrected serum calcium >11.5 mg/100 ml) that can be attributed solely to the plasma cell proliferative disorder

* Note clarification to IMWG criteria for coding CR and VGPR in patients in whom the only measurable disease is by serum FLC levels: CR in such patients is defined as a normal FLC ratio of 0.26–1.65 in addition to CR criteria listed above. VGPR in such patients is defined as a >90% decrease in the difference between involved and uninvolved free light chain (FLC) levels.
All response categories (CR, sCR, VGPR and PR) require two consecutive assessments made at any time before the institution of any new therapy; complete, PR and SD categories also require no known evidence of progressive or new bone lesions if radiographic studies were performed. Radiographic studies are not required to satisfy these response requirements. Bone marrow assessments need not be confirmed.
** for progressive disease, serum M-component increases of ≥1 gm/100 ml are sufficient to define relapse if starting M-component is ≥5 gm/100ml.

Appendix 5: Estimated Glomerular Filtration Rate (eGFR)

eGFR is the estimated glomerular filtration rate calculated by the abbreviated MDRD equation:

$186 \times (Creat/88.4)^{-1.154} \times (age)^{-0.203} \times (0.742 \text{ if female}) \times (1.210 \text{ if black})$

If you have an eGFR calculated by your local laboratory, use that as it will take into account local variations in creatinine measurements. If this is not done, below is a link to an eGFR calculator which you can use to calculate eGFR to determine any dose reductions.

eGFR Calculator:
www.renal.org/eGFRcalc/

Appendix 6: CTCAE Grading for Common Infections

Adverse Event	1	2	3	4	5
Lung Infection	-	Moderate symptoms; oral intervention indicated (e.g., antibiotic, antifungal, antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; radiologic, endoscopic, or operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Soft Tissue Infection	-	Localized; local intervention indicated (e.g., topical antibiotic, antifungal, or antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; radiologic or operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Urinary Infection	-	Localized; local intervention indicated (e.g., topical antibiotic, antifungal, or antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; radiologic or operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Sepsis	-	-	-	Life-threatening consequences; urgent intervention indicated	Death

Appendix 7: EUROQOL© (EQ-5D) Quality of Life Questionnaire

Here are some simple questions about your health in general. By ticking one answer in each group below, please indicate which statements best describe your own health state TODAY.

(Please circle one number)

1. Mobility

I have no problems in walking about	1
I have some problems in walking about	2
I am confined to bed	3

2. Self-care

I have no problems with self-care	1
I have some problems washing or dressing myself	2
I am unable to wash or dress myself	3

3. Usual Activities

I have no problems with performing my usual activities *(e.g. work, study, housework, family or leisure activities)*	1
I have some problems with performing my usual activities	2
I am unable to perform my usual activities	3

4. Pain/Discomfort

I have no pain or discomfort	1
I have moderate pain or discomfort	2
I have extreme pain or discomfort	3

5. Anxiety/Depression

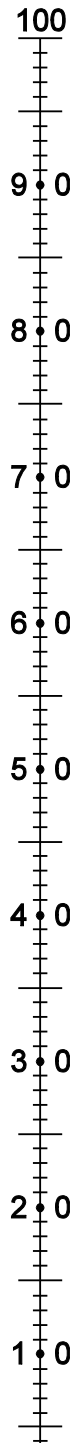
I am not anxious or depressed	1
I am moderately anxious or depressed	2
I am extremely anxious or depressed	3

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

Your own health state today

Best imaginable health state



Worst imaginable health state