Early **s**w**i**tch to oral antibiotic therapy in patient**s** **wit**h low risk neutropeni**c** sepsis.

Acronym: The **EASI-SWITCH** Trial

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Logo:

PROTOCOL AUTHORISATION

Protocol Title	Early switch to oral antibiotic therapy in patients with low risk neutropenic sepsis.
Protocol Acronym (if applicable)	The **EASI-SWITCH** trial
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Protocol Amendments	**v1.0-v2.0 – v1.0** was never approved for use. v2.0 incorporated changes to section 8.3 regarding IMP as requested by MHRA. **V2.0-3.0** Incorporated changes to eligibility criteria **V3.0 -4.0** incorporated changes to Pilot phase timeline **V4.0 -5.0** incorporated further changes to eligibility criteria
	V4.0-v5.0 key changes; 1 Study Summary: Study Aim & Objectives 1 Study Summary: Primary Outcome 1 Study Summary: Key Secondary Outcomes 1 Study Summary: Inclusion Criteria 6.3.2 Secondary Objectives 7.3 Study Timeline 8.2.1 Inclusion Criteria 8.4.2 Secondary Outcome Measures 10.6.5 Additional Analyses

A review of the protocol has been completed and is understood and approved by the following:

VICTORIA COYLE		31 / 08 / 2016
Chief Investigator Name	Signature	Date
CIÚNA McDOWELL	Ciúna McDowell	30 / 08 / 2016
Statistician	Signature	Date

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LIST OF ABBREVIATIONS

Abbreviation / Acronym	Full Wording
ADL	Activities of daily living
AE	Adverse Event
ALT	Alanine aminotransferase
ANC	Absolute neutrophil count
AR	Adverse Reaction
AST	Aspartate aminotransferase
AUC	Area under the curve
BHSCT	Belfast Health and Social Care Trust
BP	Blood pressure
CEA	Cost effectiveness analysis
CI	Chief Investigator
% CI	% confidence interval
COMET	Core outcome measures in effectiveness trials
CONSORT	Consolidated standards of reporting trials
CRF	Case Report Form
CRP	C-reactive protein
CSF	Colony stimulating factor
CTA	Clinical Trial Authorisations
CTCAE	Common Terminology Criteria for Adverse Events
CTU	Clinical Trials Unit
CUA	Cost-utility analysis
CVAD	Central venous access device
CVC	Central venous catheter
DMEC	Data Monitoring and Ethics Committee
DMP	Data management plan
EDTA	Ethylenediaminetetraacetic acid
ELISA	Enzyme-linked immunosorbent assay
ESMO	European Society for Medical Oncology
EU	European Union
EudraCT	European Clinical Trials Database
GCP	Good Clinical Practice
GDG	Guideline development group
HDU	High dependency unit
HR	Heart rate
HRQoL	Health related quality of life
HTA	Health Technology Assessment
IB	Investigator brochure
ICH	International Conference of Harmonisation
ICU	Intensive care unit
IL	Interleukin

IMP	Investigational Medicinal Product
ISF	Investigator site file
ISRCTN	International Standard Randomised Controlled Trial Number Register
IV	Intravenous
MASCC	Multinational Association of Supportive Care in Cancer
mCTA	Model clinical trial agreement
MHRA	Medicine and Healthcare Products Regulatory Agency
MRSA	Methicillin-resistant Staphylococcus aureus
NCEPOD	National Confidential Enquiry into Patient Outcome and Death
NICE	National Institute for Health and Care Excellence
NICTU	Northern Ireland Clinical Trials Unit
NIHR	National Institute for Health Research
NS	Neutropenic sepsis
PCR	Polymerase chain reaction
PCT	Pro-calcitonin
PI	Principal Investigator
PPI	Patient public involvement
ProADM	Pro-adrenomedullin
QALY	Quality adjusted life year
REC	Research ethics committee
ROC	Receiver operating characteristic
RR	Respiratory rate
SACT	Systemic anti-cancer treatment
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAR	Serious Adverse Reaction
SDV	Source data verification
SOP	Standard operating procedure
SPC	Summary of Product Characteristics
SSTI	Skin and soft tissue infection
SUSAR	Suspected Unexpected Serious Adverse Reaction
TMF	Trial master file
TMG	Trial Management Group
TSC	Trial Steering Committee
UAR	Unexpected adverse reaction
ULN	Upper level of normal

1 STUDY SUMMARY

Scientific title	**Ea**rly **s**w**i**tch to oral antibiotic therapy in patient**s** **wit**h low risk neutropeni**c** sepsis: a randomised, controlled, non-inferiority trial with allocation concealment. Acronym: The EASI-SWITCH Trial
Public title	**Ea**rly **s**w**i**tch to oral antibiotics in patient**s** **wi**th low risk neutropenic sepsis
Health condition(s) or problem(s) studied	Neutropenic sepsis (NS)
Study Design	Interventional study comparing whether early switch to oral antibiotics 12-24 hours after intravenous antibiotic treatment commences in patients with low risk neutropenic sepsis is non-inferior to standard care. This is a phase IV randomised, controlled, non-inferiority trial with allocation concealment. Both arms of the trial will be conducted in parallel.
Study Aim and Objectives	**Aim** To establish the clinical and cost-effectiveness of early switch to oral antibiotics, 12-24 hours after intravenous antibiotic treatment commences in low risk cancer patients with neutropenic sepsis. **Primary objective** The primary objective is to determine whether early switch to oral antibiotic therapy is non-inferior to current standard care, in terms of treatment failure. **Secondary objectives** Secondary objectives are to assess the effect of early switch to oral antibiotics on: (i) Short-term change in health-related quality of life, using EQ-5D-5L as the measurement tool, at baseline and 14 days. (ii) Cost-effectiveness, based on the cost per treatment failure avoided at 14 days and a cost-utility analysis (CUA) estimating the cost per quality adjusted life year (QALY) at 14 days. (iii) Time to resolution of fever from initial IV antibiotic administration. (iv) Adverse events related to antibiotics. (v) Hospital discharge and total length of hospital stay. (vi) Readmission to hospital within 28 days. (vii) Death within 28 days.

	(viii) Adjustment to the subsequent scheduled cycle of chemotherapy within 28 days. (ix) Patient preferences for antibiotic treatment assessed at day 14.
Study Intervention	**Intervention:** Switch to oral ciprofloxacin & co-amoxiclav, 12-24 hours after starting intravenous therapy with standard dose piperacillin/tazobactam or meropenem for at least 5 days total antibiotic treatment. **Standard care:** Intravenous therapy with standard dose piperacillin/tazobactam or meropenem for at least 48 hours (later discontinuation +/- oral antibiotic switch at physician discretion).
Primary Outcome	Treatment failure defined as one or more of the following criteria are met by day 14: (i) Persistence, recurrence, or new onset of fever (temperature ≥38^{o}C) after 72hrs of starting intravenous antibiotic treatment (ii) physician-directed escalation from protocol antibiotic treatment (iii) re-admission to hospital (related to infection or antibiotic treatment) (iv) critical care admission (v) death
Key Secondary Outcomes	(i) Change in health-related quality of life based on EQ-5D-5L at baseline and 14 days. (ii) Cost-effectiveness of early switch compared to standard care at 14 days. (iii) Time to resolution of fever from initial IV antibiotic administration (iv) Adverse events related to antibiotics (v) Duration of hospital admission (vi) Readmission to hospital within 28 days (vii) Death within 28 days (viii) Adjustment to the subsequent scheduled cycle of chemotherapy within 28 days. (ix) Patient preferences for antibiotic treatment
Exploratory objective	Identification of potential biomarkers for risk stratification in NS
Key Inclusion and Exclusion Criteria	**Inclusion criteria** (i) age over 16 years (ii) receiving SACT for a diagnosis of cancer (iii) started on empirical intravenous

	piperacillin/tazobactam or meropenem, for suspected NS, for less than 24 hours (iv) Absolute neutrophil count ≤1.0x10^9/L with <u>either</u> a temperature of at least 38^{o}C <u>or</u> other signs or symptoms consistent with clinically significant sepsis e.g. hypothermia. Self-measurement at home or earlier hospital assessment of temperature are acceptable provided this is documented in medical notes and is within 24 hours prior to IV antibiotic administration. (v) expected duration of neutropenia <7 days (vi) low risk of complications using a validated risk score (MASCC score ≥21) (vii) able to maintain adequate oral intake and take oral medication (viii) adequate hepatic (AST &/or ALT <5xULN) and renal function (serum creatinine <3 x ULN) within 24 hours prior to randomisation (ix) physician in charge of care willing to follow either the intervention or standard care protocol per randomisation, at enrolment, including not **treating** with colony stimulating factor (CSF). Prophylactic use of CSF is not an exclusion criterion. **<u>Exclusion criteria</u>** (i) underlying diagnosis of acute leukaemia or haematopoietic stem cell transplant (ii) hypotension (systolic pressure <90mmHg on >1 measurement) within the 24 hours prior to randomisation (iii) prior allergy, serious adverse reaction, or contra-indication to any study drug (iv) enrolled in this trial with prior episode of neutropenic sepsis (v) previously documented as being colonised with an organism resistant to a study drug regimen e.g. MRSA (vi) localising signs of severe infection (pneumonia, soft tissue infection, central-venous access device infection, presence of purulent collection) (vii) patients unable to provide informed consent (viii) pregnant women, women who have not yet reached the menopause (no menses for ≥ 12 months without an alternative medical cause) who test

	positive for pregnancy, are unwilling to take a pregnancy test prior to trial entry or are unwilling to undertake adequate precautions to prevent pregnancy for the duration of the trial. (ix) breastfeeding women
Countries of Recruitment	Northern Ireland, England, Scotland and Wales
Study Setting	UK NHS Cancer Centres/Cancer Units that deliver SACT and/or manage complications arising from SACT
Target Sample Size	628
Study Duration	Set up 3 months Pilot trial 12 months Full trial additional 30 months recruitment Analysis, follow-up and close down 6 months Unless otherwise agreed by the funder

2 STUDY TEAM

Co-Chief Investigators	Dr Victoria Coyle Dr Ronan McMullan
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This study is funded as a result of a commissioned call from the NIHR and the protocol was developed in response to review by NIHR HTA.

4 ROLES AND RESPONSIBILITIES

4.1 **Contributorship**

Dr Victoria Coyle and Dr Ronan McMullan conceived the study. The grant holders; Dr Victoria Coyle, Dr Ronan McMullan, Prof Richard Wilson, Prof Danny McAuley, Prof Michael Clarke, Dr Richard Adams, Prof Rosemary Barnes, Prof Ruth Plummer, Prof Anne Thomas, Dr Ewan Brown, Dr Dawn Storey, Dr Ian Chau, Ms Evie Gardner, Dr Ashley Agus and Mrs Margaret Grayson alongside Dr Caroline Forde and Dr Nicola Goodfellow contributed to the design of the study. Evie Gardner provided statistical expertise in clinical trial design and Clíona McDowell will conduct the primary statistical analysis. Ashley Agus provided health economics expertise in clinical trial design and is conducting the primary health economics analysis. All investigators and the Trial Management Group contributed to the refinement of the study protocol and approved the final manuscript.

4.2 **Sponsor**

The Belfast Health and Social Care Trust (BHSCT) will act as Sponsor for the study and the Chief Investigator (CI) will take overall responsibility for the conduct of the trial. Separate agreements will be put in place between the Sponsor, CI and each organisation who will undertake Sponsor-delegated duties in relation to the management of the study.

4.3 **Committees**

The CI will have overall responsibility for the conduct of the study. The Clinical Trials Unit (CTU) will undertake trial management including preparing clinical trial applications (MHRA, REC and research governance), pharmacovigilance, site initiation/training, monitoring, analysis and reporting. The Trial Manager/Co-ordinator will be responsible on a day-to-day basis for overseeing and co-ordinating the work of the multi-disciplinary trial team. Additional trial specific oversight committees will be convened for the EASI-SWITCH trial, these will include a Trial Management Group (TMG), Data Monitoring and Ethics Committee (DMEC) and Trial Steering Committee (TSC). The CTU will facilitate in the setting-up and the co-ordination of these trial committees.

4.3.1 **Trial Management Group (TMG)**

A Trial Management Group (TMG) will be established and Chaired by the CI. The TMG will have representation from the CTU and other investigators/collaborators who are involved in the study and provide trial specific expertise (e.g. trial statistician). This group will have responsibility for the day to day operational management of the trial, and regular meetings of the TMG will be held to

discuss and monitor progress. The discussions of the TMG will be formally minuted and a record kept in the TMF.

A TMG Charter details the terms of reference of the TMG including membership and roles/responsibilities.

4.3.2 Trial Steering Committee (TSC)

The TSC will oversee the progress of the trial on behalf of the trial funder and sponsor. The TSC will provide overall supervision of the trial and provide advice through the Chair to the CI, Sponsor, Funder and host institution on all appropriate aspects of the trial. The TSC will concentrate on the progress of the trial, adherence to protocol, patient safety, new information of relevance to the research question, the rights, safety and wellbeing of trial participants and ensure appropriate approvals are obtained in line with the project plan. The TSC will agree proposals for substantial amendments and provide advice to the sponsor and funder regarding approvals of such amendments.

Membership of the TSC will comprise of an independent chair, the CI (or designee), independent clinicians with relevant expertise, independent statisticians/epidemiologists/diagnosticians with relevant expertise and at least one patient/public representative. The TSC will meet at least annually and will have a minimum of 75% independent members. The NIHR HTA Programme Director will vet nominees and appoint the chair and members.

A TSC charter details the terms of reference of the TSC including membership and roles/responsibilities.

4.3.3 Data Monitoring and Ethics Committee (DMEC)

The role of the DMEC is to safeguard the rights, safety and wellbeing of trial participants, monitor data and make recommendations to the TSC on whether there are any ethical or safety reasons why the trial should not continue and monitor the overall conduct of the study to ensure the validity and integrity of the study findings.

Membership of the DMEC will be completely independent and comprise experts in the field e.g. a clinician with relevant experience and a statistician. The DMEC will meet at least annually. The NIHR HTA Programme Director will vet nominees and appoint the chair and members.

A DMEC charter will be drawn up to detail the terms of reference of the DMEC including membership and roles/responsibilities. A DMEC report will be drawn up by the trial statistician to include information on any adverse events (AEs), recruitment, outcomes and any other data requested by the committee.

5 BACKGROUND AND RATIONALE

5.1 Background information

Neutropenic sepsis (NS) is a long-recognised complication of systemic anti-cancer therapy (SACT) (Bodey et al, 1966; Schimpff et al, 1971 and Pizzo et al, 1982) that is a major cause of morbidity and mortality in patients with cancer. While NS most commonly occurs following treatment with cytotoxic chemotherapy, it can also occur with more novel biological therapies. Typically the neutrophil count falls to its nadir 5 to 7 days after SACT administration and can take up to several weeks to recover, although these timelines can vary for some therapeutic agents and regimens (Holmes, 2002). NS has also been reported to occur more commonly early in the first 2 cycles of treatment (Lyman et al, 2005) and in particular treatment settings, for example, the likelihood of developing NS after adjuvant taxane and anthracycline-containing chemotherapy for breast cancer has been reported as 25 to 29% (Martin et al, 2005; Head et al, 2008). In addition to the intensity of chemotherapy, other predisposing factors include age, performance status, nutritional status and having an underlying haematological malignancy (Lyman, 2005). Therefore following SACT, there is the potential for patients to be at risk of developing overwhelming infection, and NS is universally considered to be a medical emergency. There has been an increased focus on NS in the UK in recent years with the National Confidential Enquiry into Patient Outcome and Death (NCEPOD) publication in 2008 which reviewed deaths within 30 days of SACT and identified areas for improvement of care including management of suspected NS. It should also be noted that SACT use is increasing with 60% more chemotherapy given in 2006 than in 2002 hence NS represents an increasing burden of illness to the NHS (NCAG, 2009).

5.1.1 Definition of NS

There is clear consensus on the importance of early recognition and prompt treatment with broad-spectrum antibiotics (de Naurois et al, 2010; NICE 2012) but there is much less consensus regarding the definitions of neutropenic and sepsis in this setting with no evidence comparing definitions of neutropenia or fever in patients with suspected NS (de Naurois et al, 2010; NICE, 2012; Clarke et al, 2011; Flowers et al, 2013; Ammann et al, 2003; Apostolopoulou et al, 2010; Ha et al, 2011; Hakim et al, 2010; Klaassen et al, 2000; Santolaya et al, 2001; Tezcan et al, 2006; West et al, 2004). On review of the limited evidence, the NICE Guideline Development Group (GDG) concluded that using values of 0.5 for ANC and 38°C for temperature for diagnosis of NS represented an acceptable balance between overdiagnosis/overtreatment and missing potentially life-threatening infection (NICE, 2012). In the NHS, NS care pathways commonly use a temperature threshold of ≥38^{o}C and an absolute neutrophil count threshold of either ≤0.5x10^{9}/L or <1.0x10^{9}/L and falling/expected to fall.

5.1.2 Management of NS

Most consensus practice guidelines recommend admission and empirical broad-spectrum intravenous antibiotics in patients presenting with fever following anti-cancer therapy (de Naurois, 2010; NICE, 2012). However there is much less consensus on patient management thereafter including duration of treatment, time to switch from intravenous to oral antibiotics and duration of hospital admission. The majority of UK cancer centres treat patients with empirical intravenous therapy either until treatment is complete or switch to oral therapy at a variable time-point during treatment with treatment durations of up to 10 days reported in a previous survey of UK clinicians who treat NS (Innes et al, 2005). Duration of hospital admission was also variable in this survey with

no clear consensus regarding criterion for discharging patients and most clinicians making decisions based on arbitrary thresholds for temperature and neutrophil count.

5.1.2.1 Choice of empirical intravenous antibiotic therapy in NS

The backbone of empirical antibiotic therapy for NS for many years was a beta-lactam antibiotic in combination with an aminoglycoside. With the advent of newer generation beta-lactams with broader spectrums of activity, including an anti-Pseudomonas effect, it was postulated that monotherapy could provide adequate treatment for NS. A systematic review based on 71 studies concluded that there was no difference in the risk of all-cause mortality for monotherapy compared with combination therapy (Paul et al, 2013), with similar results for trials comparing the same beta-lactam in both arms and for trials comparing different beta-lactams (typically a broad-spectrum agent as monotherapy and a less broad spectrum agent in combination with an aminoglycoside). The treatment failure rate was greater with monotherapy but adverse events were more likely with combination therapy, in particular, nephrotoxicity, and there was no correlation between mortality rates and failure rates. Evidence for an effect on quality of life or duration of hospital admission is not available however the available data suggests that monotherapy is more cost-effective than combination treatment (Paladino et al, 2000; Corapcioglu and Sarper, 2005).

Despite this the NICE GDG noted that there was still widespread use of combination regimens with reasons for aminoglycoside use cited as concerns about secondary infection with *Clostridium difficile* and promotion of antibiotic resistance by monotherapy. Local resistance patterns also influence choice of agent(s) due to resistance to beta lactam monotherapy. The GDG recommended that patients with suspected NS should be offered beta lactam antibiotic monotherapy with piperacillin/tazobactam as initial empiric treatment, unless there were local microbiological contraindications. Similarly, it was recommended that an aminoglycoside, either in mono or dual antibiotic therapy should not be used for the initial empiric treatment unless there were local microbiological indications (NICE, 2012).

5.1.2.2 Duration of empirical intravenous antibiotic treatment

The lack of prospective evidence to support a specific duration of treatment is notable with NICE recommending that empiric antibiotics are continued in patients with persistent fever but that these could be discontinued in patients showing evidence of clinical response regardless of ANC.

NICE recommends the principle of switching to oral antibiotics based on risk assessment after 48 hours of intravenous therapy however this recommendation is constrained by the lack of high quality clinical trial evidence and as a result. oral switch at this time-point is not mandated in the NICE guidelines but is reflected in variability of current clinical practice with many patients receiving longer courses of intravenous antibiotic. Similarly the European Society for Medical Oncology (ESMO) guidance does not specify a duration of treatment but suggests that if the patient is asymptomatic and has been apyrexic for 48 hours, the ANC is $\geq 0.5 \times 10^9$/L and blood cultures are negative then antibiotics can be discontinued (de Naurois et al, 2010).

5.1.3 **Risk stratification in NS**

It is widely accepted that patients with NS are a heterogenous group. Although rates of major complications such as documented infection or admission to critical care of 25-30% and mortality rates of up to 11% have been reported in some patient groups (Kuderer et al, 2006), at the other end

of this spectrum are patients without clear evidence of clinical or microbiologically-confirmed infection who are at low risk of complications but who effectively receive overtreatment with associated distress to the patient and burden to the healthcare system (Leese, 1993; Rubenstein et al, 1993). Clearly the ability to identify patient-reported symptoms, clinical features or laboratory parameters predictive of serious complications would enable better risk stratification and treatment of patients with NS. However, evidence is lacking to support the use of specific symptoms experienced by patients in the community prior to presentation to secondary care as predictors of poorer outcomes. (Ammann et al, 2003, 2004 and 2010; Chayakulkeeree et al, 2003; Hakim et al, 2010; Klaassen et al, 2010 and Klastersky et al, 2000). There is stronger evidence to support use of risk scores that combine a number of clinical factors for predicting risk of complications, in particular for the identification of those patients at low risk of infective complications, in whom treatment could potentially be de-intensified to oral antibiotic therapy or outpatient treatment.

5.1.3.1 Risk stratification by clinical risk score:

Several clinical prediction algorithms have been independently developed for the identification of cancer patients with low risk NS (Elting et al, 1997; Rackoff et al, 1996; Talcott et al, 1988 and Talcott et al, 1992 and Viscoli et al, 1994). There is limited validation of these prediction tools with trials largely small in size and single centre. In an attempt to obtain an internationally validated, simple and reliable clinical prediction rule to identify patients with low risk NS who would be suitable for a de-intensification of treatment, the Multinational Association of Supportive Care in Cancer (MASCC) undertook a multinational, multicentre, prospective observational study of adult patients with NS (Klastersky et al, 2000). Over 40 factors potentially predictive of serious complications were evaluated from 1139 episodes of NS split into a training set of 756 and a test set of 353. All patients met the following criteria: an ANC less than $0.5x10^9$/L, a temperature greater than 38°C and received empirical treatment with an appropriate initial broad-spectrum antibiotic regimen. In the training set, independent factors predictive of a low risk of complications were weighted to develop a risk-index score (Table 1). On testing in the validation set, a risk-index score of 21 or greater identified low-risk patients with a positive predictive value of 91%, a sensitivity of 71% and a specificity of 68%. A low rate of adverse outcomes (6% had serious complications and 1% mortality), was observed in patients receiving standard care who had a risk index score of $\geq$21.

Table 1: MASCC risk index (Klastersky, 2000)

Characteristic	Weight
Burden of febrile neutropenia: no or mild symptoms*	5
Burden of febrile neutropenia: moderate symptoms*	3
No hypotension (systolic BP >90 mmHg)	5
No chronic obstructive pulmonary disease	4
Solid tumour or no previous fungal infection	4
No dehydration requiring parenteral fluids	3
Outpatient status	3
Age < 60 years	2

*Points attributable to the variable "burden of febrile neutropenia" are not cumulative. The maximum theoretical score is therefore 26.

The ability of the MASCC scoring system to predict patients at low risk of complications has been subsequently investigated in a number of studies (Paesmans et al, 2003; Uys et al, 2004; Cherif et al, 2006; Klastersky et al, 2006; Baskaran et al, 2008; De Souza et al, 2008; Innes et al, 2008; Ahn et al, 2011; Carmona-Bayonas et al, 2011; Hui et al, 2011). In these studies, use of a cut-off threshold for MASCC score of 21 to predict risk of serious complications, yielded a sensitivity of 40-80% and specificity 59-65%, but the majority of these studies are small, single-centre and of inconsistent methodology.

A previous UK survey identified that around 20% of clinicians used some form of risk stratification to guide treatment, initiating oral antibiotic therapy in low risk patients (Innes et al, 2005). From updated survey data submitted to the NICE CDG, while around one-third of UK clinicians now use risk stratification of patients as a routine tool for immediate identification and management of low risk patients with less intensive treatment, it was noted that there was no single risk scoring system in routine use and considerable variation in practice. NICE recommend that a validated risk scoring system such as the MASCC score for adults to assess a patients' risk of infective complications within 24 hours of presentation to secondary or tertiary care (NICE, 2012).

5.1.3.2 Risk stratification by biomarkers:

Although a number of laboratory investigations are routinely carried in patients with NS, robust biomarkers predictive of mortality, length of stay, need for critical care and documented infection are lacking. NICE have undertaken a review of the role of "routine" investigations (full blood count, electrolytes, liver function tests and inflammatory markers) in predicting infective complications and concluded that the available evidence suggested raised levels of lactate, and to a lesser extent, C-reactive protein (CRP) were indicative of an increased likelihood of severe sepsis (NICE, 2012). Whilst this finding is relevant given the routine use of these tests in clinical practice, it does not support the use of these tests for risk stratification of patients.

Similarly a recent systematic review and meta-analysis of predictive biomarkers in children and young adults with NS highlighted the inconsistency and heterogeneity of available studies. The authors were unable to recommend particular markers for routine clinical use but suggested three biomarkers, Interleukin-6 (IL6), Interleukin-8 (IL8) and pro-calcitonin (PCT), showed promise as potential predictive markers and warranted further investigation (Philips et al, 2012). There is additional evidence to support serum pro-adrenomedullin (proADM) and serum pro-calcitonin (PCT) (a marker that is already integrated into routine clinical practice in patients with suspected sepsis (Wacker et al, 2013)) as markers that may have predictive value in this patient population (Ahn et al, 2012; Ahn et al, 2013; Al Shuaibi et al, 2013; Debiane et al 2014).

While a number of these biomarkers appear promising, and indeed have been incorporated into routine clinical care for risk stratification in other infection settings, such as PCT in lower respiratory tract infection, there is insufficiently robust data to recommend their use in NS.

5.1.4 **Treatment of low risk NS with oral antibiotic therapy**

An updated Cochrane review of oral versus intravenous antibiotics for NS evaluated 22 trials comprising 3142 episodes of NS in 2372 patients with results suggesting no significant differences in treatment failure or mortality for oral in comparison with intravenous treatment (Vidal et al, 2013). The majority of studies excluded patients with acute leukaemia, haemodynamic instability, evidence of organ failure or localising signs of infection (pneumonia, CVAD infection or soft tissue infection).

These results were stable across a range of patient subgroups and were not dependent on the choice of antibiotic regimen, age of patient and whether oral therapy was upfront or sequential (oral therapy after a short period of intravenous therapy). There was a trend towards more adverse events in patients receiving oral treatment, typically gastrointestinal events (which did not necessitate treatment discontinuation).

However it must be noted that while this evidence broadly supports early use of oral antibiotics in low-risk NS, either by initial use of oral antibiotics or by early switch from intravenous to oral therapy, most currently available trials are small (n<100), often single centre, and many attract methodological concerns, meaning a robust recommendation for upfront or early oral therapy cannot be made. Similarly, the reviewers were unable to identify evidence supporting a specific oral regimen for use in NS, suggesting that combination therapy with a quinolone and an agent with activity against Gram positive organisms would be reasonable. Finally, this group recommended that further research should look at such a treatment strategy in the low risk NS population.

The NICE GDG also considered choice of oral regimen but noted that local microbiological resistance patterns vary and that antibiotic choice may be influenced by prior exposure including prophylactic therapy (for which a quinolone is typical) and consequently were unable to make a recommendation for a specific regimen. The GDG did note that in patients who did not receive antibiotic prophylaxis, quinolones with/without co-amoxiclav were the most frequently used agents (NICE, 2012).

5.1.4.1 Outpatient management of low risk NS

The NICE GDG also reviewed the evidence for inpatient versus outpatient management of NS and concluded outpatient management can be considered for selected low-risk patients taking into account clinical and social circumstances for individual patients. However, the quality of evidence was low to moderate and the available data was limited by lack of reporting of key outcomes such as critical care admission or clinically documented infection and a very low event rate for adverse outcomes including death (NICE, 2012). Similarly there is negligible literature relating to quality of life for different models of care including immediate use of oral antibiotics and non-admission to hospital with a single study suggesting role function improved more for inpatients than home care patients but that emotional function declined with hospital admission (Talcott et al, 2011).

5.1.5 **Reducing the burden of NS on patients and the NHS**

While variations in the definition and treatment of NS cause difficulty in determining accurately the burden of NS on both patients and the health care system nationally in relation to morbidity and health care utilisation it is clear this is not insignificant. The available data suggests that across England and Wales, there are at least 20 admissions due to NS per month in specialist centres and 3 per month in general hospitals (NICE, 2012). This is in line with published audit data suggesting an annual incidence of 137 episodes per million population per year based on admissions to seven hospitals in a large cancer network with a population of approximately 1.4 million. In this dataset, there were 71 hospital admissions with NS in 64 patients in a four month period with a median duration of admission of 5 days (Okera et al, 2011). De-intensification of treatment based on risk stratification is an attractive prospect in terms of reducing length of admission and healthcare utilisation costs. While this principle has been demonstrated in a previous small trial in a single UK centre evaluating oral antibiotics and early discharge in low risk patients, where the median in-

patient stay was reduced from 4 to 2 days (Innes et al, 2003), there remains a paucity of evidence to support widespread recommendation of this strategy.

5.2 Rationale for the study

There is a lack of high quality evidence to support the stratification of patients according to risk of infective complications enabling the use of less intensive treatment in the low risk subgroup. However, the available literature broadly supports this approach: current guidelines from NICE and the European Society for Medical Oncology (ESMO) recommend the principle of switching to oral antibiotics based on risk assessment. Both guidelines recommend that switching to oral antibiotics should be considered in patients deemed at low risk of complications after 48 hours of intravenous therapy. This recommendation by NICE was based on limited evidence supporting switching to oral antibiotics in low risk patients but with no consistent time point (Vidal et al, 2004) leading to NICE being unable to recommend oral switch before 48hrs (NICE, 2012). The NICE GDG noted that switching at an earlier time-point (for example 8-16 hours) would be likely to be associated with even greater gains for patients but there was no meaningful evidence to support this approach. This randomised controlled non-inferiority trial has therefore been developed to evaluate the clinical and cost effectiveness of stopping intravenous antibiotic therapy and switching to oral therapy within the first 24 hours of treatment in patients with NS who are having treatment with intravenous antibiotics. Based on the NICE GDG recommendations for such a study, the following outcomes will be measured: overtreatment, death, need for critical care, length of hospital stay, duration of fever and quality of life.

Demonstrating that treatment of low risk NS based on oral therapy is as effective as current treatment would bring a number of advantages for patients and the NHS. It is expected that such an approach would be associated with less intravenous access complications, including infection, and a shorter length of hospital admission; hence, an improvement in convenience and quality of life in this patient group is an expected benefit. There are potential benefits to the NHS in reducing healthcare utilisation including drug costs, aseptic preparation and administration time, as well as inpatient treatment costs.

5.3 Rationale for the intervention

Based on the NICE guidance, it is anticipated that all patients enrolled will be receiving either standard dose intravenous piperacillin/tazobactam or meropenem, according to local policy, at randomisation. Patients randomised to the intervention will switch to standard dose oral ciprofloxacin and co-amoxiclav 12-24 hours after intravenous treatment has been commenced. Antibiotic treatment will be continued for a minimum of 5 days in this arm. Evidence supporting this treatment strategy comes from the Cochrane review (Vidal et al, 2013): "*the combination of a quinolone and a second drug active against Gram-positive bacteria (for example ampicillin-clavulanate) seems prudent*".

5.4 Rationale for the comparator

The comparator in this study is standard care therapy which is based on NICE guidance. It is anticipated that all patients enrolled will be receiving either standard dose intravenous piperacillin/tazobactam or meropenem, according to local policy, at randomisation. Participants in the standard care arm will be allocated to continue treatment with intravenous antibiotic, until at

least 48 hours. Further antibiotic management will be at the discretion of the treating physician and may include switch to oral treatment and/or stopping antibiotics at any point thereafter. This reflects the variation in care in routine clinical practice.

6 STUDY AIM AND OBJECTIVES

6.1 **Research Hypothesis**

Early switch to oral antibiotic therapy, 12-24 hours after intravenous antibiotic treatment commences in low risk cancer patients with neutropenic sepsis (NS) is non-inferior to standard care.

6.2 **Study Aim**

To establish the clinical and cost-effectiveness of early switch to oral antibiotics, 12-24 hours after intravenous antibiotic treatment commences in low risk cancer patients with neutropenic sepsis.

6.3 **Study Objectives**

6.3.1 **Primary objective**

The primary objective is to determine whether early switch to oral antibiotic therapy is non-inferior to current standard care in terms of treatment failure.

To meet the main objective we will compare the treatment failure rate between the intervention and control arms of the trial on day 14. The definition of treatment failure in this study is a composite measure, incorporating a number of important clinical outcomes. These comprise:

(i) Persistence, recurrence or new onset of fever (temperature ≥38^{o}C) after 72hrs of starting intravenous antibiotic treatment;
(ii) physician-directed escalation from protocol antibiotic treatment;
(iii) re-admission to hospital (related to infection or antibiotic treatment);
(iv) critical care admission;
(v) death.

6.3.2 **Secondary objectives**

Secondary objectives are to assess the effect of early switch to oral antibiotics on:

(i) Short-term change in health-related quality of life, using EQ-5D-5L as the measurement tool, at baseline and 14 days.
(ii) Cost-effectiveness, based on the cost per treatment failure avoided at 14 days and a cost-utility analysis (CUA) estimating the cost per quality adjusted life year (QALY) at 14 days.
(iii) Time to resolution of fever from initial IV antibiotic administration
(iv) Adverse events related to antibiotics
(v) Hospital discharge and total length of hospital stay
(vi) Readmission to hospital within 28 days
(vii) Death within 28 days
(viii) Adjustment to the subsequent scheduled cycle of chemotherapy within 28 days.
(ix) Patient preferences for antibiotic treatment assessed at day 14

6.3.3 **Exploratory objective**

Future identification of potential biomarkers for risk stratification in NS

7 STUDY DESIGN

7.1 Study Design

This study is a randomised, controlled, non-inferiority trial with allocation-concealment. Early switch to oral antibiotics, 12-24 hours after intravenous treatment commences, will be compared to standard care, which comprises intravenous treatment for at least 48 hours. Eligible participants will be randomised (with randomly permuted blocks) in a 1:1 ratio to the intervention and standard care groups, using an automated system, to ensure allocation concealment. In order to assess the clinical effectiveness of the intervention based on the primary outcome, after allowing for potential participant crossover and drop out, 628 patients will be recruited.

7.1.1 Internal pilot study

An internal study to confirm both recruitment and adherence assumptions that have contributed to study design will precede the main trial. This will continue for 12 months and will be conducted at 4-8 sites. Recruitment will halt at the end of the pilot study to enable review of the study and a decision on progression to be made. The main parameters of interest, to guide the progress of the trial and inform the procedures to be used in it's delivery, are: recruitment rates; adherence to the protocol-specified intervention; and separation in terms of timing of the antibiotic switch between the two arms

The parameters that will be used to determine whether progression to full trial continues, including our proposed progression criteria are:

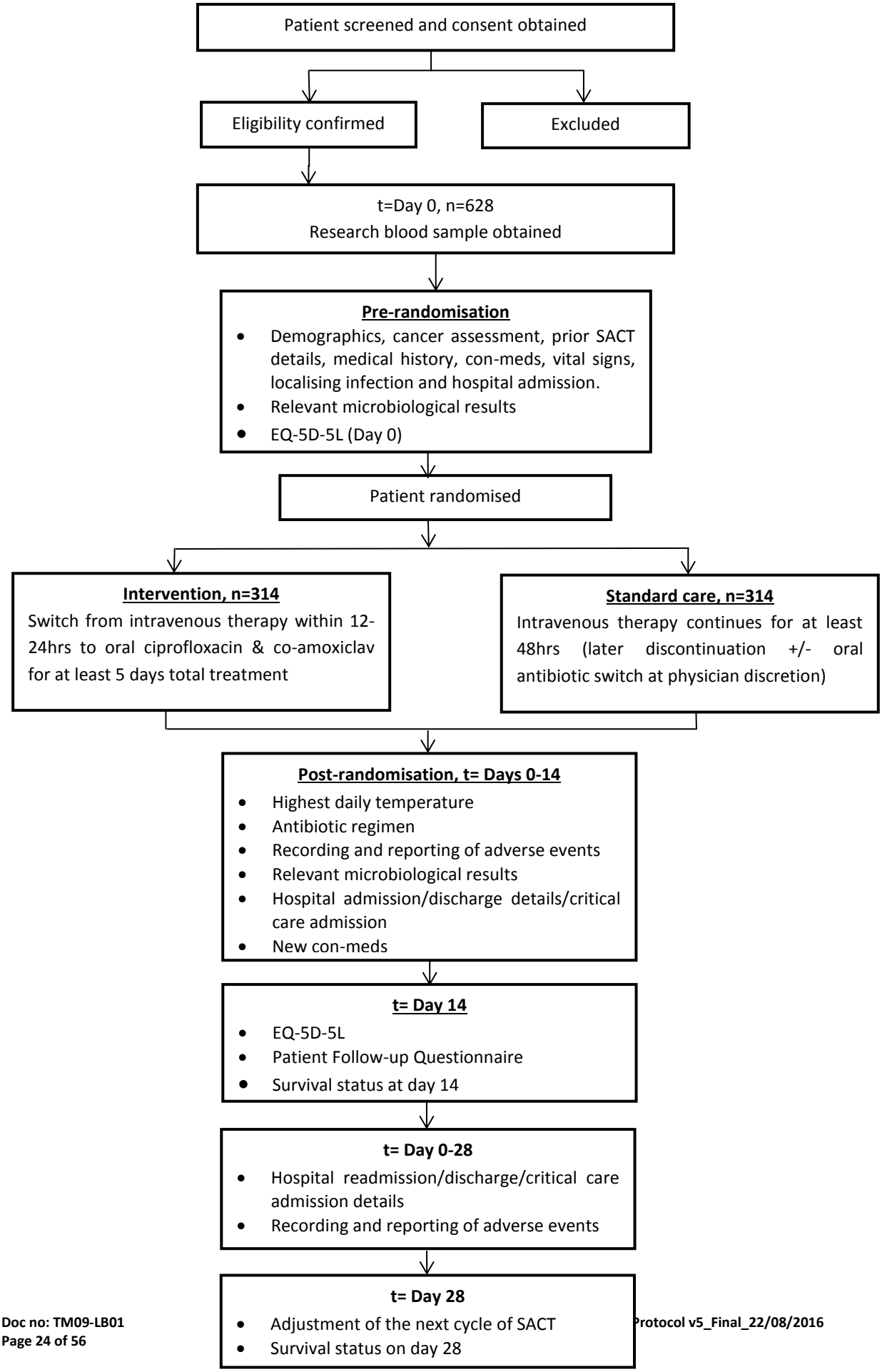
(i) Recruitment rate (the expected recruitment rate is 1.7 patients per site per month with a 50% reduction for the first three months of site opening):
   a. progression without major modification if at least 75% of target reached, with analysis and resolution of any identified barriers to successful recruitment.
   b. progression with addition of further trial sites if between 50-75% of target reached.
   c. progression unlikely if less than 50% of target reached – this equates to, on average, 4 patients per site over the 12 month pilot period. This would be subject to detailed review of project viability by the Trial Steering Committee and HTA team.

(ii) Adherence to protocol-specified intervention:
   a. progression without major modification if at least 75% adherence in both trial arms. This will be supported by a site reported self-assessment, and subsequent resolution, of barriers to adherence in proceeding to full trial if adherence is less than 90% in either arm
   b. if adherence is between 50-75% of target reached, progression will be supported by a detailed analysis of the process and decision-points that led to non-adherence. Progression to full trial will be enabled only if a means to improve adherence can be readily identified by this analysis and supported by HTA
   c. progression unlikely if less than 50% adherence in either arm.

(iii) Separation, in terms of the intervention, between the arms:
   Separation in terms of the timing of antibiotic switch of at least 24hrs between the trial arms to enable progression is required.

Participants enrolled in the pilot will be included in the analysis of the main study.

7.2 Study Schematic Diagram



7.3 **Study Timeline**

Year		1				2				3				4				5
Quarter		1	2	3	4	1	2	3	4	1	2	3	4	1	2	3	4	1
Period End		3	6	9	12	15	18	21	24	27	30	33	36	39	42	45	48	51
Trial stage	Pre-grant	Set up	Pilot Trial				Main Trial										Analysis Reporting	
Recruit Staff	X	X																
Ethics approval	X	X																
MHRA approval	X	X																
R&D approvals	X	X	X	X		X	X	X										
Contracting	X	X	X	X														
Site Training	X	X	X	X		X	X											
Patient Recruitment			X	X		X	X	X	X	X	X	X	X	X	X	X		
Patient accrual						34	82	142	202	263	324	385	446	507	568	628		
Data Entry			X	X		X	X	X	X	X	X	X	X	X	X	X	X	
HRQoL Follow-up			X	X		X	X	X	X	X	X	X	X	X	X	X	X	
Patient Follow-up				X		X	X	X	X	X	X	X	X	X	X	X	X	
Trial Management Group meetings	X2	X3	X3	X3	X3	X3	X3	X3	X3	X3	X3	X3	X3	X3	X3	X3	X3	X3
Trial Steering Committee		X		X				X				X				X		
DMEC		X		X				X				X				X		
Site Close Down																	X	
Health Economic analysis																	X	X
Final data Analysis																	X	X
Trial Report																		X
Dissemination																		X

7.4 End of Study

The end of trial will be when database lock occurs for the final study analysis. The study will be stopped early if;

1. Mandated by the research ethics committee
2. Mandated by Sponsor
3. Mandated by regulatory authorities
4. Recommended by the TSC
5. If funding ceases

8 METHODS: participants, interventions, and outcomes

8.1 Study Setting

Patients will be recruited from sites across England, Scotland, Wales and N. Ireland, comprising both large cancer centres and cancer units, to ensure that the sample is broadly representative of patients developing NS in the UK. A list of study sites will be maintained in the TMF and can be obtained from the NICTU.

8.2 Eligibility Criteria

Patients at each site with NS will be screened daily for eligibility (against the inclusion/exclusion criteria), within 24 hours of starting intravenous treatment, by the research team. Patients meeting these criteria will then be discussed with their treating physician on that day prior to enrolment to confirm their agreement to patient participation. This will also provide an opportunity to confirm that their treating physician would be willing to follow the treatment strategy outlined in either arm of the trial, including not prescribing colony stimulating factor. Eligibility to participate in the trial will be confirmed by a medically qualified doctor who has been delegated by the PI to carry out this function. The medically qualified doctor confirming eligibility must sign the eligibility checklist to document this review and confirm that the patient is eligible. This eligibility checklist will be filed in the patient notes. Randomisation will be completed by an appropriately trained and delegated member of the research team.

Patients will be eligible to participate in the study if they fulfil the following inclusion criteria and no exclusion criteria:

8.2.1 Inclusion criteria

(i) age over 16 years

(ii) receiving SACT for a diagnosis of cancer

(iii) started on empirical intravenous piperacillin/tazobactam or meropenem, for suspected NS, for less than 24 hours

(iv) Absolute neutrophil count ≤1.0x10^9/L L with either a temperature of at least 38^{o}C or other signs or symptoms consistent with clinically significant sepsis e.g. hypothermia.
Self-measurement at home or earlier hospital assessment of temperature are acceptable provided this is documented in medical notes and is within 24 hours prior to IV antibiotic administration.

(v) expected duration of neutropenia <7 days

(vi) low risk of complications using a validated risk score (MASCC score ≥21)
(vii) able to maintain adequate oral intake and take oral medication
(viii) adequate hepatic (AST &/or ALT <5xULN) and renal function (serum creatinine <3 x ULN) within the 24 hours prior to randomisation
(ix) physician in charge of care willing to follow either the intervention or standard care protocol per randomisation, at enrolment, including not treating with colony stimulating factor (CSF). Prophylactic CSF is not an exclusion criterion.

8.2.2 Exclusion criteria

(i) underlying diagnosis of acute leukaemia or haematopoietic stem cell transplant
(ii) hypotension (systolic pressure <90mmHg on >1 measurement) within the 24 hours prior to randomisation
(iii) prior allergy, serious adverse reaction, or contra-indication to any study drug
(iv) enrolled in this trial with prior episode of neutropenic sepsis
(v) previously documented as being colonised with an organism resistant to a study drug regimen e.g. MRSA
(vi) localising signs of severe infection (pneumonia, soft tissue infection, central-venous access device infection, presence of purulent collection)
(vii) patients unable to provide informed consent
(viii) pregnant women, women who have not yet reached the menopause (no menses for ≥ 12 months without an alternative medical cause) who test positive for pregnancy, are unwilling to take a pregnancy test prior to trial entry or are unwilling to undertake adequate precautions to prevent pregnancy for the duration of the trial.
(ix) breastfeeding women

8.2.3 Co-enrolment guidelines

Patients currently enrolled in other Phase I investigational medicinal product (IMP) studies and other anti-microbial IMP studies will be excluded.

Patients enrolled in other phase II-IV IMP or observational studies are potential candidates for this study. This is at the PI's discretion and should be considered when the burden on participants is not expected to be onerous.

Co-enrolment with any studies should be documented in the CRF. Although co-enrolment may be permitted under the EASI-SWITCH protocol, the co-enrolled trial protocol must also be consulted.

8.2.4 Trial centre requirements

The main trial will take place in UK NHS Cancer Centres/Cancer Units that deliver SACT and/or manage complications arising from SACT. These centres must have experience in the delivery of cancer clinical trials and access to this patient population with sufficient infrastructure support to screen, recruit, consent and randomise patients within 24hrs of starting intravenous therapy for NS (including the ability to obtain blood, plasma and serum from patients at enrolment, process and store at -80^{o}C in accordance with trial specific procedures). Treating physicians responsible for management of patients with NS at each centre must agree to maintain trial allocation in patients randomised by their colleagues.

8.2.5 **Research Team Requirements**

Staff must demonstrate and document a willingness to comply with the protocol, standard operating procedures, trial specific procedures, the principles of GCP (Good Clinical Practice) and regulatory requirements and be prepared to participate in locally-delivered trial-specific training.

8.3 **Interventions**

8.3.1 **Intervention description**

In the NHS, it is usual that neutropenic cancer patients who present to hospital with fever are admitted for intravenous antibiotic treatment, though the duration of hospitalisation is variable. Patients will be screened, consented and randomised within 24 hours of starting intravenous antibiotic treatment, however, the setting of care will not be specified by the protocol. Local customary practice, as well as arrangements for adequate clinical management and follow-up facilitating discharge, are expected to vary between sites and will influence the timing of discharge at each site. This will enable physicians to choose the most appropriate care setting for their patients, within the requirement to provide both adequate clinical care and follow-up to enable complete data collection.

It is anticipated that all patients enrolled will be receiving either standard dose intravenous piperacillin/tazobactam or meropenem, according to local policy and SPC, at randomisation. This is based on the trial inclusion/exclusion criteria, current national guidance and the applicants' collective experience. No patients in either arm will be treated with colony-stimulating factor for neutropenic sepsis, nevertheless, prophylactic colony stimulating factor administered prior to the current episode of neutropenic sepsis is not an exclusion criterion.

Participants in the standard care arm will be allocated to continue treatment with intravenous antibiotic, for at least 48 hours. Further antibiotic management will be at the discretion of the treating physician and may include a switch to oral treatment and/or stopping antibiotics at any point thereafter.

Participants randomised to the intervention arm will be switched from intravenous antibiotic treatment (12-24 hours after starting intravenous treatment) to oral antibiotic treatment. The timepoint of oral switch will be defined as the time at which the final dose of intravenous antibiotic is administered. The time of the first oral dose of antibiotic administered in the intervention group should be recorded in the medical notes, if possible this should occur in hospital.

8.3.1.1 IMP details

The following medicines are regarded as Investigational Medicinal Products (IMPs) for the purposes of this trial:
Ciprofloxacin tablets
Co-amoxiclav tablets
Piperacillin/tazobactam powder for solution for infusion
Meropenem powder for solution for injection or infusion

The IMPs for this study are UK licensed drugs. Ciprofloxacin and co-amoxiclav are only considered to be an IMP if the patient is randomised to the intervention arm; if ciprofloxacin and/or co-amoxiclav

are prescribed in the standard care arm these will not be considered to be IMPs. IMPs will not be supplied by the Sponsor. Routine hospital stock will be used and will be supplied and labelled in accordance with usual clinical practice. Local arrangements for recording supply, receipt, storage, dispensing, administration, accountability, return and destruction of hospital stock will apply.

Prior to randomisation participants will be receiving treatment with piperacillin/tazobactam or meropenem as per standard care. Participants randomised to the standard care group will continue to receive piperacillin/tazobactam or meropenem for a minimum of 48 hours. Participants randomised to the intervention group will continue to receive piperacillin/tazobactam or meropenem for a maximum of 24 hours. The dosing regimen will be in accordance with the SPC and local policy/guidelines.

Participants randomised to the intervention group will receive oral ciprofloxacin 750mg twice daily and co-amoxiclav 625mg three times daily to complete at least 5 days total antibiotic treatment by their treating physician.

The 750mg dose of ciprofloxacin may be provided in the following strength combinations:
1. Ciprofloxacin 500mg and 250mg tablets
2. Ciprofloxacin 250mg tablets
3. Ciprofloxacin 750mg tablets

The choice of oral antibiotic regimen for the intervention arm was guided by the recent Cochrane review recommendation for oral therapy (Vidal et al, 2013): "*the combination of a quinolone and a second drug active against Gram-positive bacteria (for example ampicillin-clavulanate) seems prudent*".

A minimum duration of five days treatment for the intervention is specified because:

(i) patients whose fever resolves within 48hrs of switch to oral antibiotics (i.e. within 72hrs of starting antibiotic treatment), they will receive at least 48hrs of treatment after becoming afebrile, which is expected to be sufficient.

(ii) patients whose fever does not resolve within 48hrs of switch to oral antibiotics (i.e. within 72hrs of starting antibiotic treatment), they will have reached the primary endpoint of treatment failure. Their treatment will no longer follow study protocol but locally-determined standard practice, as directed by their attending physician.

8.3.2 **Intervention discontinuation**

There is no provision to amend the allocated intervention without reaching the primary endpoint of treatment failure. Participants' treating physicians may, at their discretion, amend the dose, prematurely stop the intervention and/or start further antibiotic treatment. If a participant's physician judges such a change to the intervention as necessary for a participant, that participant will have reached the primary endpoint (treatment failure) and their treatment will no longer be protocolised.

8.3.3 **Intervention adherence**

Study drug administered while participants are inpatients will be recorded by nursing staff on hospital medication charts which will be reviewed by the site research team. For those participants discharged home with a supply of oral IMP they will be asked to note doses taken on a patient diary and asked to post this back to the research team. This information will be recorded on the CRF by the study site research nurse.

8.3.4 **Concomitant care**

Colony-Stimulating Factor (CSF) is prohibited in both trial arms. Participants receiving this treatment after randomisation, before the day 28 outcome evaluation, will be excluded from the analysis. Prophylactic colony stimulating factor administered prior to the current episode of neutropenic sepsis is not an exclusion criterion.

Systemic antibiotic treatment other than study drug will be prohibited in the intervention arm after randomisation. Systemic antibiotic administered prior to randomisation is not a reason for exclusion. If such treatment is started after randomisation and before the day 14 outcome evaluation that participant will be categorised as having met the primary endpoint of treatment failure.

8.3.5 **Exploratory biomarker analyses**

Venous blood will be collected from patients recruited to the trial on the day of randomisation. Research blood samples will be handled according to a study specific laboratory manual.

A whole blood sample (approx. 8 ml) will be collected in EDTA blood collection tubes and a further sample (approx. 4 ml) collected in a blood collection tube. Whole blood will be aliquoted and plasma and serum obtained following centrifugation and aliquoted on site. These whole blood, plasma and serum samples will be frozen, batched and transported to Belfast for central analysis to include the following:

(i) Detection of a range of bacterial/fungal pathogens will be completed on whole blood samples using a multiplex PCR assay.

(ii) For analysis of interleukin-6 (IL-6), interleukin-8 (IL-8), proadrenomedullin (proADM) and procalcitonin (PCT), serum samples will be thawed and biomarker levels measured in accordance with previously reported methods (ELISA).

Specimens will be tested retrospectively in batches, such that the results of these assays will be unavailable to clinical teams in real-time and will not influence patient care. The laboratory analysis will be completed by an assessor to whom neither patient nor their clinical outcome (i.e. the reference standard) will be known.

8.4 **Outcome Measures**

8.4.1 **Primary Outcome Measure**

The primary outcome to be used is a composite measure of treatment failure; this will be assessed at 14 days after starting intravenous antibiotics for the treatment of NS, in keeping with the NIHR commissioning brief. This will enable an assessment of the clinical effectiveness of the intervention, in comparison with standard care. The constituents of this composite are all considered to be 'in the same direction' – in other words, it is reasonable to expect that all would be more likely in the

intervention arm. While the lack of a COMET- endorsed core outcome set is disappointing, there is widespread support for the composite measure proposed, as outlined below.

The primary outcome of treatment failure will be defined by any one of:

(i) Persistence, recurrence, or new onset of fever (temperature ≥38^{o}C) after 72hrs of intravenous antibiotic initiation
(ii) physician-directed escalation from protocol-specified antibiotic treatment
(iii) re-admission to hospital (related to infection or antibiotic treatment)
(iv) admission to critical care
(v) death

This primary outcome was determined based on:

(i) the important outcomes specified in the NIHR commissioning brief
(ii) published guidelines from an international expert consensus relating to trials in NS supporting use of a 72hr fever resolution timepoint (within the primary endpoint) [Feld et al., 2002]
(iii) these guidelines also support use of a composite measure to define treatment success/failure that accounts for a range of possible adverse outcomes (including both infection and antimicrobial treatment-related events). Also, use of a composite primary outcome features in almost all reported NS trials of antimicrobial therapy.
(iv) advice from our patient representatives that the constituents of the composite are all of importance to patients.
(v) site investigator experience

8.4.2 **Secondary Outcome Measures**

The secondary outcomes have been selected to support the assessment of clinical and cost effectiveness of early oral antibiotic switch. The following will be assessed on day 14:

(i) time to resolution of fever from initial IV antibiotic administration;
(ii) adverse events due to antibiotics or their route of administration;
(iii) hospital resource utilisation, including length of hospitalisation;
(iv) health- related quality of life;
(v) cost-effectiveness. The cost- effectiveness analysis, consistent with the primary outcome measure, will be performed to estimate the cost per treatment failure avoided at 14 days and a cost-utility analysis will estimate the cost per quality adjusted life year (QALY) at 14 days.
(vi) patient preferences for antibiotic treatment

Further secondary outcomes, comprising readmission to hospital (related to infection or antibiotic treatment), change in subsequent planned SACT and death, will be assessed on day 28.

8.4.3 **Exploratory objective**

The identification of potential biomarkers for risk stratification in neutropenic sepsis.

8.5 **Participant Timeline**

Table: Schedule of enrolment, interventions and assessments

Table adapted from Chan A-W, Tetzlaff JM, Gøtzsche PC, *et al.* SPIRIT 2013 Explanation and Elaboration: Guidance for protocols of clinical trials. *BMJ* 2013;346:e7586.

		STUDY PERIOD						
		t-24hrs		Day 0	Study visits and procedures			
	TIMEPOINTS	*Pre-consent (standard care)*	*Pre-randomisation*	*Randomisation*	*Day 1-2*	*Day 3-5*	*Day 6-14*	*Day 28*
Pre-enrolment	**PRE-CONSENT ELGILBILITY SCREENING**							
	Eligibility screening as appropriate (per standard care) e.g. Absolute neutrophil count, Blood sample[‡] Blood culture[†] *as per standard care*	X X						
	Informed consent							
	Informed consent obtained		X					
	PRE-RANDOMISATION ELGIBILITY & ASSESSEMENTS							
	Eligibility screening as appropriate (non-standard care) e.g. pregnancy test, MASCC score, max temp within 24 hours prior to randomisation.		X					
	EQ-5D-5L		X					
	RANDOMISATION							
	Standard care antibiotic administration*	X	X	X	X	X		
	Intervention (*early switch*) antibiotic administration*	X	X	X	X	X		
	Research whole blood sample[±]			X				
	Send GP letter			X				
	BASELINE ASSESSMENTS TO BE RECORDED ON CRF AFTER ELIGIBILITY IS CONFIRMED							
	Demographics		X					
	Vital signs (*HR, RR and BP*)		X					
	Medical history		X					
	Symptoms indicative of mild localised infection		X					
	Cancer assessment**		X					
	SACT administered prior to presentation[#]		X					
	Relevant microbiological results		X	X	X	X	X	
	Hospital admission details		X					
	Concomitant medications		X	X	X	X	X	
	DAILY DATA COLLECTION							
	Antibiotic regimen[‡‡]	X	X	X	X	X	X	
	Highest daily temperature[%]	X	X	X	X	X	X	
	PROTOCOL COMPLIANCE							
	Adherence to protocol specified intervention				X	X		
	PATIENT FOLLOW-UP							
	EQ-5D-5L						X	
	Patient Follow-up Questionnaire						X	
	Follow-up contact						X	X
	Survival status						X	X
	New medications						X	
	Changes to next planned SACT							X
	Hospital discharge/re-admission/critical care admission details			X	X	X	X	X
	Recording and reporting of adverse events		X	X	X	X	X	X

**IV antibiotics will commence prior to informed consent*
†Date taken, positive or negative, organism(s)
‡As a minimum AST or ALT and serum creatinine will be documented and reviewed for eligibility. When available the following standard care blood results should also be recorded– Hb, platelets, CRP, albumin, lactate.
***Cancer type, treatment intent (Radical, Adjunctive, Palliative), line of treatment (1st, 2nd or 3rd)*
#Date, regimen and cycle number
%Highest daily temperature whilst inpatient or temperature recorded if unwell as an outpatient
±Whole blood, plasma and serum sample to be stored at -80°C. Research blood sample may be taken at any time on the day of randomisation after consent has been obtained.
‡‡Route, dose (strength & frequency), antibiotic name

Patients may be contacted by phone if discharged from hospital to collect data on day 14 and 28 endpoints +/- 1 day. GP may be contacted to provide treatment information, hospital admission, AE and mortality data.

8.6 **Sample Size**

The required sample size is 628 patients. This is based on an assumed 15% treatment failure rate in the standard care arm and a non-inferiority margin of 10%, at 90% power (1-sided 97.5% confidence interval), which requires 269 patients per arm. We have also accounted for up to a 5% dropout rate, based on: (i) data from 19 previously reported small RCTs in NS; (ii) the typically healthcare-compliant behaviour of cancer patients; and (iii) the short duration of follow-up. Furthermore, the sample size calculation includes inflation to allow for up to 10% crossover from control to intervention arm, giving 314 participants per arm (628 in total).

The estimated 15% treatment failure rate in the control arm was derived from:

(i) a prospective UK single centre trial in which the treatment failure rate was 10% (6 of 60 patients) in the intravenous arm
(ii) a 16.1% treatment failure rate (29/180 patients) in two other trials of oral switch after 48- 72 hours intravenous treatment that were reviewed by the NICE guideline group.

Collectively, there were 35/240 (14.6%) treatment failure events in these three studies. These data, of all available NS studies, are considered to best reflect the control arm in the proposed trial, based on both the similarity of the population studied (given our inclusion/exclusion criteria) and the duration of intravenous treatment administered.

8.6.1 **Justification for using a 10% non-inferiority margin**

The non-inferiority margin was set at 10% based on:
(a) the recommendation from a published expert consensus to use a 10% margin in trials of antimicrobial therapy among patients with neutropenic sepsis;
(b) advice from our patient representatives that, even if up to an extra 10 per 100 patients' treatment may fail as a result of the intervention (in addition to the expected 15 treatment failures), this would be greatly outweighed by the advantage of 75 patients having successful oral treatment – often at home. In other words, a considerable overall gain in quality of life is expected within this margin. In balancing this 'trade-off' the following were considered:

(i) the main consequence of treatment failure, highlighted in a Cochrane review, is prolonged symptoms requiring further hospital-delivered intravenous treatment
(ii) mortality in neutropenic sepsis is low overall (3%), with no reported deaths in published

trials that recruited only low risk patients, as we propose here

(iii) no association between mortality and oral antibiotic therapy noted in the Cochrane review.

8.7 Recruitment

8.7.1 Recruitment strategy

Recruitment rates have been based on the typical number of patients admitted to a specialist cancer centre with neutropenic sepsis which NICE estimates at over 20 per month (NICE, 2012). This is consistent with previously reported incidence data of 137 per million of population per year (Okera et al, 2011) and also audit data collected in the Belfast, Leicester and Newcastle sites. Therefore, even after allowing for exclusion of high risk patients (one third of admissions (Okera et al, 2011)) and the exclusion criteria we have specified (up to a further 25%), this gives approximately 10 eligible patients admitted to each site per month. Recruiting 2 of these 10 eligible patients is a conservative and achievable projection.

We plan to recruit from at least 12 large cancer centres and cancer units. The recruitment targets set have been based on the assumption that, during the first three months of recruitment, each site will recruit at only 70% of the projected full rate. The recruitment schedule is based on recruitment of 20 patients per month. This, on average, amounts to 1.7 patients per site per month. In practical terms, this is expected to equate to 2 patients for each of the large cancer centres and 1 patient for each of the cancer units, per month.

Additionally, the planned internal pilot study is intended to confirm the feasibility of the trial including screening and recruitment rates; these parameters will be critical in progression to full study.

Awareness of the trial among patients receiving treatment for cancer before they present with neutropenic sepsis will be raised by displaying study-specific posters at sites where systemic anti-cancer therapy is delivered, as well as in the associated units where these patients are admitted with treatment complications, as appropriate. A short information leaflet has also been prepared in collaboration with our PPI advisors for distribution to prospective patients when receiving a chemotherapy regimen that is expected to subsequently cause neutropenia.

8.7.2 Screening procedure

Patients treated with intravenous antibiotics for NS at each study site will be screened daily by research nurses, for eligibility against the inclusion/exclusion criteria, within 24 hours of starting intravenous antibiotic treatment. Eligible patients will then be discussed with their treating physician on that day to confirm their agreement with trial enrolment and willingness to follow the treatment strategy allocated in either arm of the trial (including non-use of colony-stimulating factor).

A screening log will be maintained at each site that will include data on the numbers of patients whose eligibility was reviewed and will detail eligibility, consent, randomisation and if applicable reasons for non-enrollment. Recording this information is required to establish an unbiased study population and for reporting according to the CONSORT statement (Moher et al, 2010).

8.7.3 **Informed consent procedure**

It is the responsibility of the Principal Investigator (or designee) to obtain written informed consent from each participant prior to entry into the trial. The Investigator (or designee) taking informed consent must be GCP trained, suitably qualified and experienced and have been delegated this duty by the Principal Investigator on the delegation log.

Only the standard care procedures indicated in the schedule of assessments (section 8.5) will be conducted prior to taking consent from the participant.

Informed consent for participation will be sought from patients by appropriately trained research nurses and medically trained investigators who will be supported in this by both a PI and other local infrastructure at each site. Where patients require further clarification about the benefits and risks of participating, this will be provided by either the research team or an independent senior physician (one will be nominated in advance for each trial site).

In view of the inclusion criteria and the timing of the intervention, informed consent will be obtained in the acute care setting hence patients must be competent to give informed consent for participation without deferring to a representative. It is envisaged that enrolled participants will have this capacity because:

(i) Enrolment will occur at ward level rather than pre-hospital or in the emergency department. Therefore, patients will have been admitted to hospital for several hours before being approached and will be clinically stable.

(ii) The inclusion/exclusion criteria specify that only low risk patients are recruited. Therefore, by definition, the most severely ill subgroup of patients will be excluded; such patients are least likely to have capacity to provide consent hence their exclusion from the trial minimises this risk.

(iii) Patients who are unable to provide informed consent, for any reason, will not be recruited as well as those who indicate that they are unable or unwilling to make a decision within the 24 hour period after starting IV antibiotics.

Participant information sheets have been prepared in collaboration with our patient representatives to summarise the possible benefits and risks.

8.7.4 **Withdrawal of consent**

Participants may withdraw or be withdrawn (by the treating physician responsible for their care) from the study at any time without prejudice. In the event that the participant is withdrawn during protocolised treatment, the clinician responsible for their care will determine the safest and most appropriate ongoing management strategy.

In the event of a request to withdraw from the study, the researcher will complete a withdrawal of consent form and determine which elements of the study are to be withdrawn:

- Protocol-specified antibiotic therapy

- All future data collection or;
    - 14 day follow-up
    - 28 day follow-up
    - Research blood sample analysis and sample storage

In the event that the participant requests withdrawal from all parts of the study, only anonymised data recorded up to the point of withdrawal will be included in the study analysis.

Participants may be withdrawn from the study at the discretion of the Investigator due to safety concerns.

9 METHODS: Assignment of interventions

9.1 Sequence Generation

Eligible participants will be allocated to intervention or standard care groups using an automated randomisation system. Blocked randomisation with randomly permuted block sizes will be used and a 1:1 allocation ratio. There are no factors for stratification. The randomisation sequence will be saved in a restricted section of the TMF which will only be able to be accessed by statisticians and not site staff who enrol or assign interventions.

9.2 Allocation Concealment Mechanism

The randomisation sequence will be concealed using a number of measures including;

i) using an automated randomisation system
ii) restricting access to the randomisation sequence

9.3 Allocation Implementation

The trial statistician will generate the allocation sequence.

When the research team at each study site identifies a patient suitable for enrolment, they will obtain informed consent for participation in the trial. Treatment allocation will be assigned using an automated randomisation process that each site research team will complete. The research team will then ensure that participants and care providers are informed which treatment has been allocated by this process. They will liaise with care providers as required to ensure that the allocated treatment is administered.

9.4 Blinding

Only the allocation of the intervention will be blinded, once assigned to the standard care or intervention group the interventions will be unblinded to the trial participants, research team, care providers, data analysts and outcome assessors. The pragmatic nature of this trial is such that blinding participants and care providers would restrict the opportunity to measure the care delivery consequences of the intervention. Furthermore, PPI advice received is that participants are highly likely to reveal their treatment allocation discussion with outcome assessors that any attempt to blind this group would be subverted.

10 METHODS: Data collection, management and analysis

10.1 **Data Quality**

The Chief Investigator (CI) and/or NICTU will provide training to site staff on trial processes and procedures including CRF completion and data collection. Within the NICTU the clinical data management process is governed by Standard Operating Procedures which help ensure standardisation and adherence to International Conference of Harmonisation Good Clinical Practice (ICH-GCP) guidelines and regulatory requirements.

On-site monitoring visits during the trial will check the accuracy of CRF entries against source documents alongside adherence to the protocol, trial specific procedures and Good Clinical Practice (GCP). This monitoring will be carried out as per the trial specific monitoring plan.

Changes to data will be recorded and fully auditable. Data errors will be documented and corrective actions implemented.

Data validation will be implemented and discrepancy reports will be generated following data entry to identify data that may be out of range, inconsistent or protocol deviations based on data validation checks programmed into the clinical trial database.

A Data Monitoring & Ethics Committee (DMEC) will be convened for the study to carry out reviews of the study data at intervals during the study.

10.2 **Data Collection**

All data collected for a participant will be performed by delegated members of the research team and recorded in the CRF, patient diary and study questionnaires. Each participant will be allocated a unique Participant Study Number at randomisation, and this, alongside their initials will be used to identify participants for the duration of the trial. Data will be collected from the time of trial entry until day 28 (+/- 1 day) thereafter. If the participant is transferred, or admitted, to another hospital the trial team will liaise with the receiving hospital to ensure complete data capture.

Data is to be entered onto the electronic database as per the CRF entry timelines.

Baseline data collection will occur in the hospital setting. Primary and secondary outcome data will be collected via a review of patient medical notes (including laboratory results), submission of participant questionnaires, patient diary, GP records and patient phone call (if discharged before day 28).

Participants discharged before day 14 will be asked to complete a diary noting administration of oral antibiotics, any new medications and a temperature diary until day 14 (as required). The Patient Follow-up Questionnaire and EQ-5D-5L will either be administered face-to-face or via telephone (if discharged) at day 14 (+/-1 day).

10.2.1 **Screening / Baseline Visit and Procedures**

Study assessments are summarised in the schedule of assessments in section 8.5.

The following will be completed as part of standard care prior to obtaining consent;

- Eligibility screening as per standard care (e.g. absolute neutrophil count, blood sample)
- Blood culture as per standard care
- Standard care IV piperacillin/tazobactam or meropenem administration

Informed consent obtained

The following will be completed at pre-randomisation;

- Eligibility assessment including any non-standard care assessments (e.g. pregnancy test, MASCC score) and confirmation of eligibility
- EQ-5D-5L

Research blood sample (12ml) to be taken on day of randomisation, after eligibility is confirmed and consent to donate blood samples for research is provided.

Randomisation and treatment allocation

- Prescribing of appropriate treatment regimen
- Send GP letter

Assessments relating to baseline data (before randomisation) are to be recorded on the CRF after eligibility is confirmed;

- Baseline characteristics (demographics, cancer assessment, medical history, vital signs)
- SACT administered prior to presentation
- Symptoms indicative of mild localised infection
- Relevant microbiological results e.g. sputum, urine sample
- Hospital admission details
- Concomitant medications

Daily data collection (day 0-14);

- Antibiotic regimen
- Highest daily temperature (in-patient) or temperature if feeling unwell (if out-patient)

Completed as appropriate throughout study after enrolment until day 28;

- Recording and reporting of AEs
- Hospital discharge/readmission details/critical care admission

10.2.2 **Study Visits and Procedures**

Day 0-14

- Highest daily temperature (in-patient) or temperature if feeling unwell (if out-patient)
- Antibiotic regimen
- Recording of any relevant microbiological results e.g. sputum, urine sample
- EQ-5D-5L on day 14 (+1 day window)
- Patient Follow-up Questionnaire on day 14 (+1 day window)

- Survival status at day 14
- New con-meds

Prior to discharge (if applicable)

- Check standard care training on taking temperature and patient has a thermometer
- Provide patient diary
- Provide discharge medication

10.2.3 **End of Study Visit and Procedures**

Day 28

- Survival status at day 28
- Adjustment to the next due SACT

10.3 **Study Instruments**

EQ-5D-5L

The EQ-5D-5L (Herdman et al, 2011) is a generic preference-based measure of health which provides a description of health using five dimensions (mobility, self-care, usual activities, pain/discomfort and anxiety/depression) each with 5 levels of severity. Responses are converted to an overall utility score which will be used for the calculation of quality adjusted life years (QALYs). Respondents are also asked to place their health on a visual analogue scale (VAS) where 0 represents the worst imaginable health state and 100 the best imaginable health state. It is recommended by NICE (NICE, 2013) for use in economic evaluations.

Patient Follow-up Questionnaire

It is acknowledged that the EQ-5D-5L will measure only the potential effect on health of an early switch from IV to oral antibiotics and will not reflect patients' preferences for non-health effects of the intervention, such as early discharge from hospital. Thus a trial specific questionnaire administered at day 14 will explore patients' preferences for the two treatment strategies under study in terms of both health and non-health related effects. The questionnaire will be piloted in the pilot trial.

MASCC

NICE recommend that a validated risk scoring system such as the MASCC score for adults to assess a patients' risk of infective complications within 24 hours of presentation to secondary or tertiary care (NICE, 2012). Using the MASCC, a risk-index score of 21 or greater identified low-risk patients with a positive predictive value of 91%, a sensitivity of 71% and a specificity of 68%. Additionally, a low rate of adverse outcomes (6% had serious complications and 1% mortality), was observed in patients who had a risk index score of $\geq$21.

Table: MASCC risk index (Klastersky, 2000)

Characteristic	Weight
Burden of febrile neutropenia: no or mild symptoms[1]	5
Burden of febrile neutropenia: moderate symptoms[2]	3

No hypotension (systolic BP >90 mmHg)	5
No chronic obstructive pulmonary disease[3]	4
Solid tumour or no previous fungal infection[4]	4
No dehydration requiring parenteral fluids	3
Outpatient status[5]	3
Age < 60 years	2

*Points attributable to the variable "burden of illness" are not cumulative. The maximum theoretical score is therefore 26.

[1] Burden of febrile neutropenia refers to general clinical status as influenced by the febrile neutropenic episode. It is evaluated in accordance with the following scale: no symptoms (5), mild symptoms (5), moderate symptoms (3), severe symptoms (0), moribund (0).

[2] The points attributed to the variable "burden of febrile neutropenia" are not cumulative. Thus, the maximum theoretical score is therefore 26. A score of ≥ 21 is considered low risk and a score of < 21 as high risk (positive predictive value of 91%, specificity of 68%, and sensitivity of 71%).

[3] Chronic obstructive pulmonary disease means active chronic bronchitis, emphysema, decrease in FEVs, need for oxygen therapy and/or steroids and/or bronchodilators.

[4] Previous fungal infection means demonstrated fungal infection or empirically treated suspected fungal infection.

[5] Patients who are admitted to hospital with suspected NS directly from the community outpatient setting will be classified as an outpatient when calculating the MASCC score in the EASI-SWITCH trial.

10.4 **Participant Retention and Follow-up**

Given the short duration of follow-up of 28-days, and the typically healthcare-compliant nature of cancer patients, difficulties with participant retention are not envisaged. This will be further enhanced by the option to obtain outcome data by a combination of healthcare records review and telephone interview.

In the event of a request to withdraw from the study, the researcher will complete an off study form and determine which elements of the study are to be withdrawn please see section 8.7.3 for more information.

10.5 **Data Management**

Trial data, including worksheets, diaries and questionnaires, will be entered onto a web-based Case Report Form (CRF) on a Clinical Trial Database (MACRO) by delegated site personnel and processed electronically as per CTU Standard Operating Procedures (SOPs) and the study specific Data Management Plan (DMP).

Data queries will be 'raised' electronically (MACRO) where clarification from site staff is required for data validations or missing data. Site staff will 'respond' electronically to data queries ensuring that amendments where applicable are made to the Clinical Trial Database.

All essential documentation and trial records will be stored securely and access will be restricted to authorised personnel.

All study documentation (including patient medical records) and data will be archived as per regulatory requirements and those responsible for archiving will be noted on the sponsor delegation framework/mCTA.

10.6 **Data Analysis**

10.6.1 **Analysis population**

Primary analysis will be conducted on all outcome data obtained from all participants as randomised and regardless of protocol adherence, i.e. intention to treat analysis. Per-protocol analysis will also be conducted which will involve a comparison of treatment groups that includes only those patients who completed the treatment originally allocated.

In view of the risk of bias arising from either analysis alone in a non-inferiority trial, we will conclude that non-inferiority of the intervention has been proven only if it is demonstrated in both analyses. This conservative approach minimises the risk of wrongly concluding non-inferiority.

10.6.2 **Statistical methods**

Analyses will be 1-sided and at a significance level of 0.025. The difference in treatment failure rate (97.5% CI) will be compared to the non-inferiority margin of 10%.

As this is a non-inferiority trial the null hypothesis is that the degree of inferiority of the intervention to the control is greater than the non-inferiority margin of 10%. The alternative hypothesis is therefore that the intervention is inferior to the control by less than the non-inferiority margin of 10%. Therefore non-inferiority is established by showing that the upper bound of a one-sided 97.5% confidence interval for Control-Intervention is < 10%.

A secondary comparison of the primary and other binary outcomes between the two groups will be investigated using logistic regression, adjusting for covariates (such as extent of neutropenia). Comparison of continuous outcomes between the two groups will be investigated using independent t-tests or Mann-Whitney. Statistical diagnostic methods will be used to check for violations of the assumptions, and transformations will be performed where required.

Baseline characteristics, follow-up measurements and safety data will be described using appropriate descriptive summary measures depending on the scale of measurement and distribution.

A detailed Statistical Analysis Plan will be written by the trial statistician prior to the final analysis.

10.6.3 **Health economics evaluation**

A within-trial economic evaluation will be performed to assess the cost-effectiveness of early switch to oral antibiotics compared with usual care in the treatment of neutropenic sepsis in patients with cancer. Thus a cost-effectiveness analysis (CEA) consistent with the primary outcome measure will be carried out to estimate the cost per treatment failure avoided at day 14 and a cost-utility analysis (CUA) will estimate the cost per quality adjusted life year (QALY) at day 14. Patients' use of hospital resources will be collected over the study period on the case-report form using data from the day 14 interview and review of medical records. This will include treatments and medication received during the primary admission and associated readmissions. Costs will be calculated by attaching appropriate unit costs from publicly available sources (e.g. Department of Health National Schedule of Reference Costs). The final year of data collection will be taken as the cost year. The EQ-5D-5L (Section 10.3) will be administered at baseline and day 14. If patients have been discharged before

day 14 the validated telephone version will be administered. If patients remain in hospital at day 14 they will self-complete the face-to-face version.The derived health state utility values at baseline and 14 days will be used in the calculation of QALYs. All analyses will be adjusted for baseline utility / health-related quality of life and other covariates where appropriate. Standard methods will be used to explore and display uncertainty in the cost-effectiveness data. Sensitivity analysis will be performed to assess the robustness of the cost-effectiveness analysis to changes in key parameters.

It is acknowledged that the EQ-5D-5L will measure only the potential effect on health of an early switch from IV to oral antibiotics and will not reflect patients' preferences for non-health effects of the intervention, such as early discharge from hospital. Thus the Patient Follow-up Questionnaire will collect additional information on this.

Full details of the health economics analysis will be incorporated in to the Statistical Analysis Plan.

10.6.4 **Exploratory biomarker analyses**

Samples will be stored and analysed in batches retrospectively both to improve methodological consistency and to minimise the cost of testing. Test results will not be available to the treating physician and will not impact upon treatment decisions for patients recruited to the study.

The diagnostic performance of each marker for predicting response to treatment for NS will be evaluated using the reference standard for treatment failure. This will include measurements for IL-6, IL-8, proADM and PCT which will be continuous data, assessed by constructing a receiver operating characteristic (ROC) curve for each test for which the area under the curve (AUC) will be estimated. AUCs of each test will be compared using non-parametric methods based on Mann-Whitney U statistics for two group comparisons and Kruskal-Wallis tests for multigroup comparisons. An optimal cut-off value for each assay will be established, based on the balance between sensitivity and specificity. For this optimal cut-off value, the sensitivity, specificity, positive and negative predictive values will be derived for each test. The same four parameters will be established for the categorical data produced by the multiplex PCR test. The predictive value of each possible combination of tests will be presented in the same terms. The performance of these tests will be examined separately for patients in each arm of the EASI-SWITCH trial. The data from this diagnostic accuracy study will also be combined with the primary outcome data from the EASI-SWITCH trial in order to model how the effectiveness of the trial intervention (early oral antibiotic switch) may be enhanced if patients were selected based on the tests evaluated.

10.6.5 **Additional analyses**

In the event that non-inferiority is demonstrated for the primary outcome, a further analysis assessing superiority of the intervention will be carried out. This analysis will be 2-sided, at a significance level of 0.05, and based on the intention to treat population.

Exploratory subgroup analyses will be reported using 99% CI. Logistic regression will be used with interaction terms (treatment group by subgroup) for the following subgroups:

(i) tumour type (solid tumour vs. lymphoma)

(ii) neutrophil count at randomisation ($\leq 0.5 \times 10^9$/L vs. $>0.5 \times 10^9$/L $<1.0 \times 10^9$/L)

(iii) maximum temperature on the day of presentation (<38°C_ vs >38°C)

10.6.6 **Missing data**

Every effort will be made to minimise missing baseline and outcome data in this trial. The level and pattern of the missing data in the baseline variables and outcomes will be established by forming appropriate tables and the likely causes of any missing data will be investigated. This information will be used to determine whether the level and type of missing data has the potential to introduce bias into the analysis results for the proposed statistical methods, or substantially reduce the precision of estimates related to treatment effects. If necessary, these issues will be dealt with using multiple imputation or Bayesian methods for missing data as appropriate.

11 METHODS: Monitoring

11.1 **Interim analyses**

At the end of the pilot the following analysis will be completed;
-Recruitment rate
-Adherence to protocol-specified intervention
-Difference between standard care and intervention arms in the timing of the IV/oral antibiotic switch
The decision on whether to continue to the full trial will be based on the results of this interim analysis.

Treatment failure rate and 95% Confidence Interval (CI) will be estimated from the pilot data for the standard care arm. If the estimated 15% treatment failure rate in the standard care arm is not within the 95% CI of the observed rate in the pilot, a sample size recalculation will be performed and the effect that this would have on progression will be estimated prior to seeking approval from the HTA to proceed to full trial.

11.2 **Definition of Adverse Events**

Table: Terms and Definitions for Adverse Events

Term	Definition
Adverse Event (AE)	Any untoward medical occurrence in a participant to whom a medicinal product has been administered, including occurrences which are not necessarily caused by or related to that product.
Adverse Reaction (AR)	Any untoward and unintended response in a participant to an investigational medicinal product, **which is related** to any dose administered to that participant.
Unexpected adverse reaction (UAR)	An adverse reaction the nature and severity of which is not consistent with the information about the medicinal product in question set out in the: Summary of Product Characteristics in the case of a licensed

	product Investigators brochure for any other investigational product.
Serious Adverse Event (SAE), Serious Adverse Reaction (SAR) or Unexpected Serious Adverse Reaction (UAR)	Respectively, any adverse event, adverse reaction or unexpected adverse reaction that: 1. results in death: Death may occur as a result of the basic disease process. Nevertheless, all deaths occurring **within 28 days of randomisation must be treated as an SAE and reported as such.** All deaths which may be considered as related to the trial agent, regardless of the interval, must be treated as a SAR and reported as such. 2. is life-threatening: The term 'life-threatening' in the definition of 'serious' refers to an event in which the patient 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. 3. requires hospitalisation or prolongation of existing hospitalisation: hospitalisation is defined as an inpatient admission, regardless of length of stay, even if the hospitalisation is a precautionary measure for continued observation. Therefore patients do not need to be hospitalised overnight to meet the hospitalisation criteria. Hospitalisation (including for an elective procedure) for a pre-existing condition (prior to study) entry which has not worsened does not constitute a serious experience. 4. results in persistent or significant disability or incapacity: (substantial disruption of one's ability to conduct normal life functions) 5. consists of a congenital anomaly or birth defect: (in offspring of subjects or their partners) taking the IMP regardless of time of diagnosis 'Important medical events' may also be considered serious if they jeopardise the subject or required an intervention to prevent one of the above consequences. They also include; Overdoses (accidental or intentional) Pregnancy outcome (of subject or partner) An alarming adverse experience Non-serious AEs and/or laboratory abnormalities which are listed in the trial protocol as critical to safety evaluations and requiring reporting.
Suspected Serious Adverse Reaction (SSAR)	Any adverse reaction that is classed in nature as serious and is consistent with the information about the medicinal product in question: In the case of a product with a marketing authorisation, in the summary of product characteristics (SPC) for that product. In the case of any other investigational medicinal product, in the investigator's brochure (IB) relating to the trial in

	question.
Suspected Unexpected Serious Adverse Reaction (SUSAR)	Any adverse reaction that is classed in nature as serious and is not consistent with the information about the medicinal product in question: In the case of a product with a marketing authorisation, in the Summary of Product Characteristics (SPC) for that product. In the case of any other investigational medicinal product, in the Investigator's Brochure (IB) relating to the trial in question.

11.3 **Eliciting Adverse Event Information**

The PI or designee will record all directly observed AEs and all AEs spontaneously reported by the patient that are not related to underlying medical conditions. AEs that are clearly related to SACT administration (e.g. peripheral neuropathy) do not need to be recorded; however, AEs that may be due to either SACT or NS/antibiotics (e.g. gastrointestinal adverse events) should be recorded. In addition, the patient will be asked about AEs at day 14 and day 28 following initiation of treatment.

11.4 **Assessment of Seriousness**

The PI or designee should make an assessment of seriousness. A serious adverse event is an adverse event, adverse reaction or suspected unexpected adverse reaction that:

- Results in death
- Is life-threatening
- Requires hospitalisation or prolongation of existing hospitalisation
- Results in persistent or significant disability or incapacity
- Consists of a congenital anomaly or birth defect
- Is any other important medical event(s) that carries a real, not hypothetical, risk of one of the outcomes above

11.5 **Assessment of Causality**

The PI or designee should make an assessment of causality, i.e. the extent to which it is believed that the event may be related to the study drug:

- **Not Related**: Temporal relationship of the onset of the event, relative to administration of the product, is not reasonable or another cause can by itself explain the occurrence of the event.
- **Unlikely**: Temporal relationship of the onset of the event, relative to administration of the product, is likely to have another cause which can by itself explain the occurrence of the event.
- **Possibly***: Temporal relationship of the onset of the event, relative to administration of the product, is reasonable but the event could have been due to another, equally likely cause.
- **Probably***: Temporal relationship of the onset of the event, relative to the administration of the product, is reasonable and the event is more likely explained by the product than any other cause.

- **Definitely***: Temporal relationship of the onset, relative to administration of the product, is reasonable and there is no other cause to explain the event, or a re-challenge (if feasible) is positive.

* Where an event is assessed as possibly, probably or definitely related, the event is an adverse reaction (AR).

11.6 Grading of Severity of Adverse Events

The PI or designee should make an assessment of severity for each AE. Severity is often used to describe the intensity of a specific event. This is not the same as 'seriousness'. AEs will be assessed for severity according to the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) version 4.03 by a medically qualified investigator. AEs that do not have a corresponding CTCAE term will be assessed according to the general guidelines for grading used in the CTCAE, as stated below.

Severity grade guidelines:

Grade	Severity	Description
1	Mild	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
2	Moderate	Moderate; minimal, local or non-invasive intervention indicated; limiting age-appropriate instrumental activities of daily living (ADL)*.
3	Severe	Severe or medically significant but not immediately life-threatening; hospitalisation or prolongation of hospitalisation indicated; disabling; limiting self-care ADL**.
4	Life-threatening	Life-threatening consequences; urgent intervention indicated.
5	Fatal	Death related to AE.

*Instrumental ADL refers to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.
**Self-care ADL refers to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

11.7 Assessment of Expectedness

The PI or designee is required to make an assessment of expectedness of any AEs possibly, probably or definitely related to the IMP based on the relevant SPC(s). Adverse reactions may be classed as either;

- Expected: The AR is consistent with the toxicity of the study drug listed in the SPC.
- Unexpected: The AR is not consistent with the toxicity in the SPC.

An AR may be described as 'unexpected' if it has occurred with greater frequency or severity that might otherwise have been expected.

11.8 Follow-up of Adverse Events

The AE reporting period for the trial begins upon enrolment into the trial and ends 28 days following randomisation.

All AEs assessed by the PI or designee as possibly, probably or definitely related to the study drug and all SAEs that occur during this time will be followed until they are resolved or are clearly determined to be due to a patient's stable or chronic condition or intercurrent illness(es).

Results from all blood tests completed pre-enrolment are not reportable as adverse events.

11.9 Recording and reporting of Adverse Events (AEs)

Only AEs that are not related to underlying medical conditions are to be recorded and reported. AEs that are clearly related to SACT administration (e.g. peripheral neuropathy) do not need to be recorded; however, AEs that may be due to either SACT or NS/antibiotics (e.g. gastrointestinal adverse events) should be recorded. All reportable AEs should be recorded in the patient medical notes and on the AE form within the CRF. All deaths occurring within 28 days of randomisation will be recorded and reported as an SAE regardless of the underlying pathology i.e. whether disease related or not.

An adverse reaction (AR) is an AE which is related to the administration of the study drug. All ARs must be reported on the AE form within the CRF.

An unexpected adverse reaction (UAR) is an AE which is related to the administration of the study drug and that is unexpected, in that it has not been previously reported in the current SPC. All UARs must be reported on the AE form within the CRF.

These events will be included as part of the safety analysis for the trial and do not require expedited reporting to the CTU.

11.10 Recording and reporting of Serious Adverse Events (SAEs)

A SAE is defined as an AE that fulfils one or more of the criteria for seriousness outlined in the Table: Terms and Definitions for Adverse Events. SAEs that are related to the administration of the study drug are serious adverse reactions (SARs). Suspected unexpected serious adverse reactions (SUSARs) are SAEs that are considered to be caused by the study drug and are unexpected i.e. their nature or severity is not consistent with the IB. All SAEs, SARs, SSARs and SUSARs must be reported to the CTU and recorded in the patient medical notes.

If a SAE/SAR occurs, reporting will follow the regulatory requirements as appropriate and all SUSARs will be the subject of expedited reporting. SAE/SARs will be evaluated by the PI for causality (i.e. their relationship to study drug), severity and expectedness. SAE/SARs will be reported using the SAE Form and must be reported to the CTU (via email to clinicaltrials@nictu.hscni.net) within 24 hours of becoming aware of the event. The PI should not wait until all information about the event is available before notifying the CTU of the SAE/SAR. The CTU will acknowledge receipt of the SAE form within two working days by email to the site. Information not available at the time of the initial report must be documented on a follow up SAE form. Follow up information should be sought and submitted as it becomes available. The follow up information should describe whether the event has resolved or persists, if and how it was treated and whether the patient continues on the study or has been withdrawn from treatment.

The CTU is responsible for reporting SAE/SARs to the Sponsor, ethics committee, and MHRA within the required timelines as per the regulatory requirements.

If an AR is assessed as serious and is consistent with the SPC for the IMP the PI must report the event to the CTU within 24 hours of becoming aware of the event using the SAE form.

In the event of a SUSAR occurring this should be reported immediately to the CTU as reporting timelines are applicable to both the MHRA and REC. A fatal or life threatening SUSAR must be reported within 7 calendar days after the CTU has first knowledge of such an event. Relevant follow up information should be sought and is communicated within an additional 8 days. All other SUSARs will be reported to the relevant competent authorities and research ethics committees within 15 calendar days after the knowledge of such an event.

11.11 Recording and reporting of urgent safety measures

If the PI or designee becomes aware of information that necessitates an immediate change in study procedure to protect clinical trial participants from any immediate hazard, they may act to eliminate an immediate hazard without prior approval from the REC or MHRA. However, the PI or designee should phone the MHRA Clinical Trials helpline on 02030806456 (Lines open Mon-Fri 08:30 to 16:30) and discuss the issue with a safety scientist or medical assessor immediately after an urgent safety measure has been implemented.

The PI or designee should report the urgent safety measure to the CTU within one working day of the event taking place by email to clinicaltrials@nictu.hscni.net.

The sponsor must follow-up with notification in writing within three days of the action being taken. The PI should respond to queries from the Sponsor immediately to ensure the adherence to reporting requirements to REC and MHRA.

11.12 Pregnancy reporting

Pregnancy is not considered an AE or SAE, however an abnormal outcome would be. Therefore the PI or designee must collect pregnancy information for female participants, and for females who become pregnant while their partners are participating in the trial. Consent should be obtained to follow up the pregnancy from the female partners of male participants.

The pregnancy reporting period for the trial is from the commencement of the study drug until 28 days post randomisation. The PI or designee should complete and submit the Pregnancy Reporting Form to the CTU by email (clinicaltrials@nictu.hscni.net) within 14 days of being made aware of the pregnancy. The CTU will acknowledge receipt of the Pregnancy Reporting Form within two working days by email to the site.

Any pregnancy that occurs in a participant or participant's partner during the trial should be followed to outcome. Follow up/outcome information should be provided to the CTU as soon as it becomes available.

An unwillingness to undertake adequate precautions to prevent pregnancy for the duration of the trial will result in exclusion criteria from this study.

11.13 Data Monitoring

11.13.1 Data access

Prior to commencement of the study, the PI at each site will give permission for trial related monitoring, audits, ethics committee review and regulatory inspections, by providing direct access to source data and trial related documentation. Consent from patients for direct access to data will also be obtained. The patients' confidentiality will be maintained and will not be made publicly available to the extent permitted by the applicable laws and regulations.

11.13.2 Monitoring arrangements

The CTU will be responsible for trial monitoring. On-site monitoring visits will be conducted in accordance with the trial monitoring plan. On-site monitoring will be an on-going activity from the time of initiation until trial close-out and will comply with the principles of Good Clinical Practice (GCP) and European Union (EU) directive 2001/20/EC. The frequency and type of monitoring will be detailed in the monitoring plan and agreed by the trial Sponsor.

Before the trial starts at a participating site, an initiation visit will take place to ensure that all relevant essential documents and trial supplies are in place and that site staff are fully aware of the trial protocol and procedures. On-site monitoring visits during the trial will check the accuracy of entries on CRF's against the source documents, the adherence to the protocol, procedures and GCP, and the progress of patient recruitment and follow up.

The PI or designee should ensure that access to all trial related documents including source documents (to confirm their consistency with CRF entries) are available during monitoring visits. The extent of source data verification (SDV) will be documented in the monitoring plan.

The close out procedure at each site will commence once the final patient enrolled has completed all follow-up required by the protocol.

12 REGULATIONS, ETHICS AND GOVERNANCE

The trial will comply with the principles of GCP, the requirements and standards set out by the EU Directive 2001/20/EC and the applicable regulatory requirements in the UK, the Medicines for Human Use (Clinical Trials) Regulations 2004 and subsequent amendments and the Research Governance Framework.

12.1 Sponsorship

The Belfast Health and Social Care Trust (BHSCT) will act as Sponsor for the study and the CI will take overall responsibility for the conduct of the trial. Separate agreements will be put in place between the Sponsor, CI and each organisation who will undertake Sponsor delegation duties in relation to the management of the study.

12.2 Regulatory and Ethical Approvals

The trial will be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki. The protocol will be approved by a Research Ethics Committee.

Appropriate REC and MHRA approvals will be obtained for the study.

12.3 Protocol Amendments

The investigators will conduct the study in compliance with the protocol given approval/favourable opinion by the Ethics Committee and the regulatory authority. Changes to the protocol may require regulatory authority/ethics committee approval/favourable opinion prior to implementation, except when modification is needed to eliminate an immediate hazard(s) to patients. The CTU in collaboration with the CI and sponsor will submit all protocol modifications to the competent authority/research ethics committees for review in accordance with the governing regulations. Protocol compliance will be monitored by the CTU who will undertake site visits to ensure that the trial protocol is adhered to and that necessary paperwork (e.g. CRF's, patient consent) is being completed appropriately.

12.4 Good Clinical Practice

The trial will be carried out in accordance with the principles of the International Conference on Harmonisation Good Clinical Practice (ICH-GCP) guidelines (www.ich.org). All members of the trial team will be required to have GCP training.

12.5 Protocol Compliance

A protocol deviation is defined as an incident which deviates from the normal expectation of a particular part of the trial process. Any deviations from the protocol will be fully documented on the protocol deviation form. There is a noted exception to this whereby if the patient refuses or the site is unable to obtain the research blood/serum sample (e.g. poor veins) this will not be considered a protocol deviation but should be documented in the CRF.

A serious breach is defined as a deviation from the trial protocol or GCP which is likely to effect to a significant degree:

i) the safety or physical or mental integrity of the subjects of the trial; or
ii) the scientific value of the trial

The PI or designee is responsible for ensuring that serious breaches are reported directly to the Sponsor within one working day of becoming aware of the breach.

12.6 Patient Confidentiality

In order to maintain confidentiality, all CRF's, questionnaires, study reports and communication regarding the study will identify the patients by the assigned unique trial identifier and initials only. Databases where information will be stored will be password protected. Patient confidentiality will be maintained at every stage and will not be made publicly available to the extent permitted by the applicable laws and regulations.

12.7 Post-trial Care

Once the trial is complete, patients presenting with neutropenic sepsis will be treated according to the local NHS standard care. There are no specific post-trial provisions for participants.

12.8 Indemnity

The BHSCT will provide indemnity for any negligent harm caused to patients by the design of the research protocol through the Clinical Negligence Fund in Northern Ireland.

12.9 Data Access

Following the publication of the primary and secondary study outcomes, there may be scope for the CI in the study to conduct additional analyses on the data collected. In such instances the CI will discuss this with the TMG. In the event of publications arising from such analyses, those responsible will need to provide the CI with a copy of any intended manuscript for approval prior to submission. Authorship will need to take the format of "[name] on behalf of the Easi-switch Clinical Trial Group" or something similar which will be agreed by the TMG.

12.10 Record Retention

Archiving of essential documents will take place as outlined in the Sponsor delegation framework. The PI will be provided with an ISF by the CTU and will maintain all trial records according to GCP and the applicable regulatory requirements. The PI is responsible for archiving of essential documents at local sites in accordance with the requirements of the Sponsor and local policies. The PI has a responsibility to allow Sponsor access to archived data and can be audited by the Sponsor or competent authority on request. The Trial Master File (TMF) will be held by the CTU within the BHSCT and the essential documents that make up the TMF will be listed in an SOP. On completion of the trial, the TMF and study data will be archived by the CTU according to the applicable regulatory requirements and for up to 15 years as required by the BHSCT Sponsor. Following confirmation from the Sponsor the CTU will notify the PI when they are no longer required to maintain the files. If the PI withdraws from the responsibility of keeping the trial records, custody must be transferred to a person willing to accept responsibility and this must be documented in writing to the CTU and Sponsor.

12.11 Competing Interests

The research costs including the cost of the intervention were funded by NIHR HTA. The CI and members of the TMG have no financial or non-financial competing interests and the members of the DMEC/TSC will be asked to confirm that they have no conflict of interest. In the event that a DMEC/TSC member reports a conflict of interest, advice will be sought from the Sponsor.

13 DISSEMINATION/PUBLICATIONS

13.1 Publication Policy

The final study report will be provided by the Trial Statistician; it is anticipated that the study findings will be published in national and international peer review journals which will be led by the CI. Publications will be discussed at the TMG and will be considered on a case by case basis. This will secure a searchable compendium of these publications and make the results readily accessible to

the public and health care professionals. In addition study findings may be presented at both national and international meetings and also to appropriate patient groups.

NIHR will be acknowledged as the funder in research publications and a copy of papers will be sent to the relevant co-ordinating centre 28 days before publication.

Due to limited resources, it will be not be possible to provide each patient with a personal copy of the results of the trial. However upon request, patients involved in the trial will be provided with a lay summary of the principal study findings. The most significant results will be communicated to the public through press releases. An on-going update of the trial will also be provided on the NICTU website.

13.2 **Authorship Policy**

An author will be considered to be someone who has made a substantive intellectual contribution to the study. All investigators, Trial Statistician and relevant members of the Trial Management Group will potentially be co-authors. Collaborators will be acknowledged.

13.3 **Data Sharing Statement**

Requests for data sharing will be reviewed on an individual basis by the CI and TMG.

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