NIHR HTA Programme

11 February 2013

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THE PROBIOTICS FOR ANTIBIOTIC ASSOCIATED DIARRHOEA (PAAD) STUDY

Stage II : A double blind randomised placebo controlled trial to determine the effect of probiotics on antibiotic associated diarrhoea in care home residents.

Version 4.1, 07/09/2012

Sponsor:	Cardiff University 30-36 Newport Road Cardiff CF24 0DE United Kingdom
Sponsor ref:	**SPON1069-11**
Funder:	**Health Technology Assessment (HTA)**
Funder ref:	**08/13/24**
REC ref:	**12/WA/0057**
EudraCT ref:	**2011-006269-17**
ISCRTN ref:	**TBC**

This protocol has been authorised by:

Name	Role	Signature	Date
Professor Christopher C Butler	Chief Investigator		07/09/12
Name	**Role**	**Signature**	**Date**
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General Information This protocol describes the THE PROBIOTICS FOR ANTIBIOTIC ASSOCIATED DIARRHOEA (PAAD) STUDY, **Stage II :** A double blinded randomised placebo controlled trial to determine the effect of probiotics on Antibiotic Associated Diarrhoea (AAD) in care home residents. This protocol provides information about the procedures for entering service users into the study. The protocol should not be used as a guide, or as an aide-memoire for the treatment of other service users. Every care has been taken in drafting this protocol; however, corrections or amendments may be necessary. These will be circulated to the known Investigators in the study, but centres entering the study for the first time are advised to contact the South East Wales Trials Unit (SEWTU) in Cardiff to confirm that they have the most up-to-date version of the protocol in their possession. Problems relating to the study should be referred, in the first instance, to SEWTU.

Compliance This study will adhere to the conditions and principles which apply to all clinical trials as outlined in the Medicines for Human Use (Clinical Trials) Regulations 2004, as amended, EU Directive 2001/20/EC, EU Directive 2005/28/EC and the ICH Harmonised Tripartite Guideline for Good Clinical Practice (CPMP/ICH/135/95). It will be conducted in compliance with the protocol, the Medicines for Human Use (Clinical Trials) Regulations 2004 (SI2004/1031), as amended, the Research Governance Framework for Health and Social Care (Welsh Assembly Government November 2001 and Department of Health 2nd July 2005), the Data Protection Act 1998, and other regulatory requirements as appropriate.

Funding The PAAD Study Stage 2 study is being funded by the National Institute of Health Research (NIHR) Health Technology Assessment (HTA) program (Ref. 08-13-24).

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Please contact the Trial Manager for general queries and supply of study documentation

Randomisation:

Randomisation

When a service user is prescribed an antibiotic and eligibility has been confirmed, the next sequentially numbered study medication pack will be allocated to the service user (see section 9.6 for more details)

Clinical queries:

Clinical queries

All clinical queries should be directed to the Trial Manager who will direct the query to the most appropriate clinical person.

Tel: 029 20687606

Serious Adverse Events:

SAE reporting

Where the adverse event meets one of the serious categories, a SAE form should be completed by the care home staff and faxed to the PAAD Trial Manager within 24 hours of becoming aware of the event

(See section 12 for more details).

Fax Number: 02920 687 612

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Glossary of abbreviations

AAD	Antibiotic Associated Diarrhoea
AE	Adverse Event
AR	Adverse Reaction
BSC	Bristol Stool Chart
CDAD	*Clostridium difficile* Associated Diarrhoea
CF	Consent Form
CH	Care Home
CHS	Care Home Staff
CI	Chief Investigator
NISCHR CRC	National Institute for Social Care and Health Research - Clinical Research Centre for Wales
CRF	Case Report Form
CTA	Clinical Trials Authorisation
CTIMP	Clinical Trial of Investigational Medicinal Product
CU	Cardiff University
EudraCT	European Clinical Trials Database
GCP	Good Clinical Practice
GMS	General Medical Services
GP	General Practitioner
HCW	Health Care Workers
HE	Health Economics
HPA	Health Protection Agency
HTA	Health Technology Assessment
ICH	International Conference on Harmonization
ID	Identification
IDMC	Independent Data Monitoring Committee
IMP	Investigational Medicinal Product
ISRCTN	International Standard Randomised Controlled Trial Number

LTCF	Long Term Care Facility
MARS	Medication Administration Record Sheet
MHRA	Medicine and Healthcare products Regulatory Agency
NHS	National Health Service
NICE	National Institute for Health and Clinical Excellence
PAAD	Probiotics for Antibiotic Associated Diarrhoea
QA	Quality Assurance
QALY	Quality-adjusted Life Years
QoL	Quality of Life
QP	Qualified Person
R&D	Research and Development
RCT	Randomised Controlled Trial
REC	Research Ethics Committee
RN	Research Nurse
RO	Research Officer
RR	Pooled relative risk ratio
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
SEWTU	South East Wales Trials Unit
SIS	Service User Information Sheet
SOP	Standard Operating Procedure
SmPC	Summary Product Characteristics
SMPU	St Mary's Pharmaceutical Unit
SSA	Site Specific Assessment
SU	Service User
SUSAR	Suspected Unexpected Serious Adverse Reactions
TM	Trial Manager
TMG	Trial Management Group
TSC	Trial Steering Committee

UHB University Health Board

1 Amendment History

Pre-ethical approval

Amendment No.	Protocol version no.	Date issued	Author(s) of changes	Details of changes made
01	2.0	04/04/2012	All listed as Chief Investigator, Co-Investigators and Trial Team	Provisional approval granted by REC, with recommended amendments included. (see details in protocol)
02	3.0	18/05/2012	All listed as Chief Investigator, Co-Investigators and Trial Team	Further justification on use of service Users with mental capacity as requested by REC, together with minor changes to information documents.

Post ethical approval

Amendment No.	Protocol version no.	Date issued	Author(s) of changes	Details of changes made
01	4.1	07/09/2012	All listed as Chief Investigator, Co-Investigators and Trial Team	1)eligibility assessment to be carried out purely by the GP 2)changes to study schema for clarity 3)minor change to the exclusion criteria, removing the words “due to difficulty of administering probiotic” 4) SU without capacity already receiving a probiotic” added to exclusion criteria following ethics discussion. 5) the exclusion criteria that the SU will be assessed against and what procedures will take place for the GP to be able to assess capacity if unable to carry this task out at time of antibiotic prescription. 6) Unblinding procedure simplified to reflect if there is a need to un-blind the SU for any reason, to contact the Study

				team 7) Changes to screening, enrolment & randomisation logs to capture progression through the study; time point is anonymised; only care home will have a full list with names;only an anonymised list will be sent to SEWTU. 8) Removal of "A withdrawal CRF will be completed at the end of the 8 week follow up period". 9) Details of how to administer the study medication 10) Updated explanation on how the study medication will be supplied, requested, stored, reconciled and disposed. 11) Dose modification for toxicity changed "to reduce the daily intake to half to allow for adjustment. If the participant continues to be uncomfortable the study medication should be stopped." 12) monitor AEs and SAEs for the 8 week follow up period (i.e. not 30 days after the last does of study medication) 13)Vomiting and stomach pain have been removed from the known side effects 14) GPs will not be responsible for reporting SAEs, the PI and care home nurses will be trained to deal with SAEs 15) timeframe in which to get the samples to the lab stated; another sample should be taken if diarrhoea continues for 48 hours 16) Removal of the sentence, "From literature, probiotics are known to carry some risks, including use in patients with cancer, diabetes, broad spectrum antibiotic therapy, septicaemia, organ transplantation and abscess. The medical history will be considered in light of these risk factors, by the Research

				Nurse at the initial consenting time point, while the GP will consider these risk factors in light of the medical history of the SU at the point of randomisation." 17) Paragraph added to state that regular monitoring will take place 18) Care home staff not to witness (sign/date) consent form, research team to witness consent 19)Professional legal representative should not be participants own GP if that GP is involved in running or managing the care home
02	4.1	07/09/2012	All listed as Chief Investigator, Co-Investigators and Trial Team	Minor amendments to the patient information sheets to reflect changes to the protocol

2 Synopsis

Short title	The Probiotics for Antibiotic Associated Diarrhoea (PAAD), a randomised controlled trial
Acronym	PAAD Stage 2 RCT
Internal ref. no.	SPON1069-11
Clinical phase	III
Trial design	A multi-centre double-blinded placebo-controlled two arm individually randomised trial of the effect of probiotics on AAD in SUs of care homes.
Trial participants	Adults who are usually resident in participating nursing or dual-registered care homes in the UK who are prescribed antibiotics during the study period.
Planned sample size	400 SUs (200 per arm)
Follow-up duration	SUs will be followed up for eight weeks from the date of randomisation.
Planned trial period	24 months
Primary objective	To compare the effectiveness of probiotics vs. placebo, taken in conjunction with antibiotics, on the incidence of AAD in care home SUs.
Secondary objectives	• To compare the effectiveness of probiotics vs. placebo, taken in conjunction with antibiotics, on the duration and severity of AAD in care home SUs. • To compare the effectiveness of the probiotics vs. placebo in reducing the incidence of *C. difficile*–associated diarrhoea (CDAD) in care home SUs. • To evaluate the impact of probiotics on Quality of Life (QoL) in care home SUs. • To evaluate the cost effectiveness of probiotics for AAD in care home SUs.
Primary endpoint	Occurrence of at least one episode of AAD during the eight weeks following randomisation.
Secondary endpoints	• Proportion of stool samples positive for *Clostridium difficile* toxin A or B from SUs who develop AAD during the eight week follow-up period. • Duration, frequency and recurrence of AAD during the eight-week follow-up period. • QoL, measured using EQ-5D at the time of randomisation and each week during the eight-week follow-up period. • Recovery from illness that triggered antibiotic treatment. • Healthcare Resource Use, including GP and practice nurse consultations, other medication, procedures, investigations, hospital appointments, A&E attendances and any hospital inpatient admissions, measured at the end of the eight-week follow-up period. • Unplanned hospitalisations, including all-cause and AAD related, during

	the eight-week follow-up period. • Adverse Events: e.g. vomiting, abdominal pain, excessive flatulence, bloating, skin rashes, during the eight-week follow-up period. • Adherence to the antibiotic, probiotic/placebo treatment course. • All causes of mortality in the 8 week follow up period.
Investigational medicinal products	• VSL# 3, freeze dried lactose free sachet containing 4.4g of a mixture of 450 billion live lactic acid bacteria and bifidobacteria. These bacteria consist of eight strains of potentially beneficial bacteria: ○ *Streptococcus thermophilus,* ○ *Bifidobacterium breve,* ○ *Bifidobacterium longum,* ○ *Bifidobacterium infantis,* ○ *Lactobacillus acidophilus,* ○ *Lactobacillus plantarum,* ○ *Lactobacillus paracasei* ○ *Lactobacillus delbrueckii subsp. Bulgaricus.* Placebo Formulation (*TBC*): *A lactose free powder 4.4g Sachet*, matched for taste, consistency and colour. Dispensed as above.
Form	Freeze -dried powder
Dose	One sachet (4.4g of freeze-dried powder), twice daily
Route	*Per oral*

3 Study summary & schema

3.1 Study summary

PAAD Stage II is a multi-centre double-blinded placebo-controlled two arm individually randomised trial of the effectiveness of probiotics on AAD in SUs of care homes.

The primary objective is to assess the effect of probiotics, taken in conjunction with antibiotics, on the incidence of AAD. This will be ascertained by comparing the proportion of SUs in each arm that experience at least one episode of AAD during the eight weeks following randomisation.

We aim to randomise 400 SUs (200 per arm) from approximately 24 care homes. We aim to recruit from care homes that have at least 50 SUs in residence, but may recruit from some with fewer than 50 SUs if the recruitment potential in these care homes is considered adequate. General Practitioners (GPs) serving the recruited care homes will be fully informed of the study.

Consent will be taken at the time of enrolment to confirm, in advance, that in the event of an oral antibiotic being prescribed by a responsible clinician at any point during the subsequent year (12 months), the SU will be randomised to receive a probiotic or matched placebo. SUs and their relatives (where applicable) will be fully informed of the study using written materials and posters in care homes, supplemented with verbal explanations. Consent will be taken from SUs where they are able and willing to provide this. In the event of cognitive impairment that limits ability to provide fully informed consent, we will approach relatives and/or personal or legal representatives to provide consent on behalf of the SU to participate. It is anticipated that 607 SUs will be enrolled in order to achieve the target of 400 patients in the study.

Enrolled SUs who are prescribed an oral antibiotic in the course of usual care at any time during the following 12 months will be assessed by the GP to ensure that they remain eligible to participate in the study. If the SU is eligible they will be randomised to receive probiotics (VSL$^{\#}$3) or placebo in addition to their antibiotic prescription. SUs will be followed up for eight weeks following randomisation.

3.2 Study schema Participant Flow Diagram

Figure 1. Study Schema

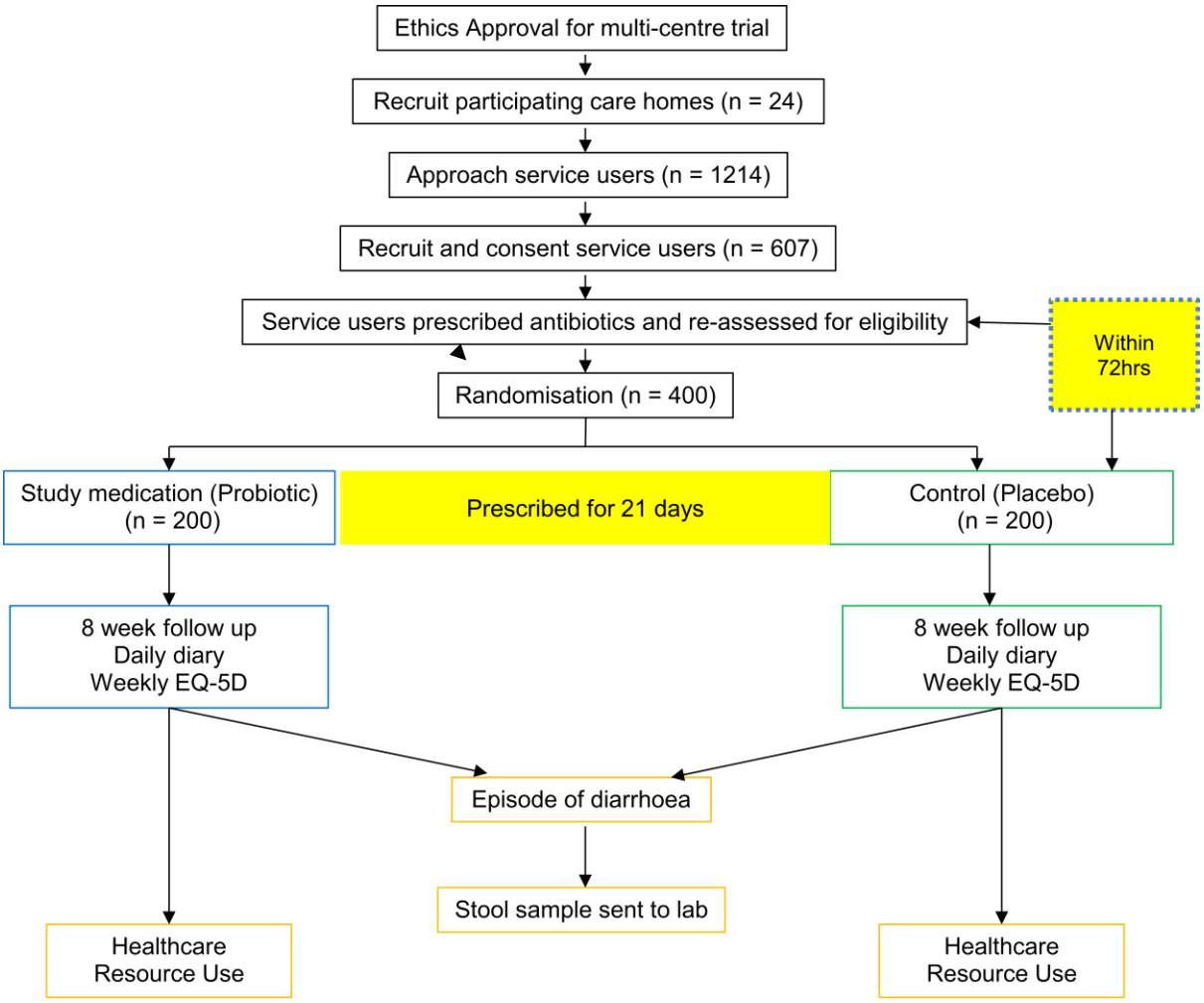
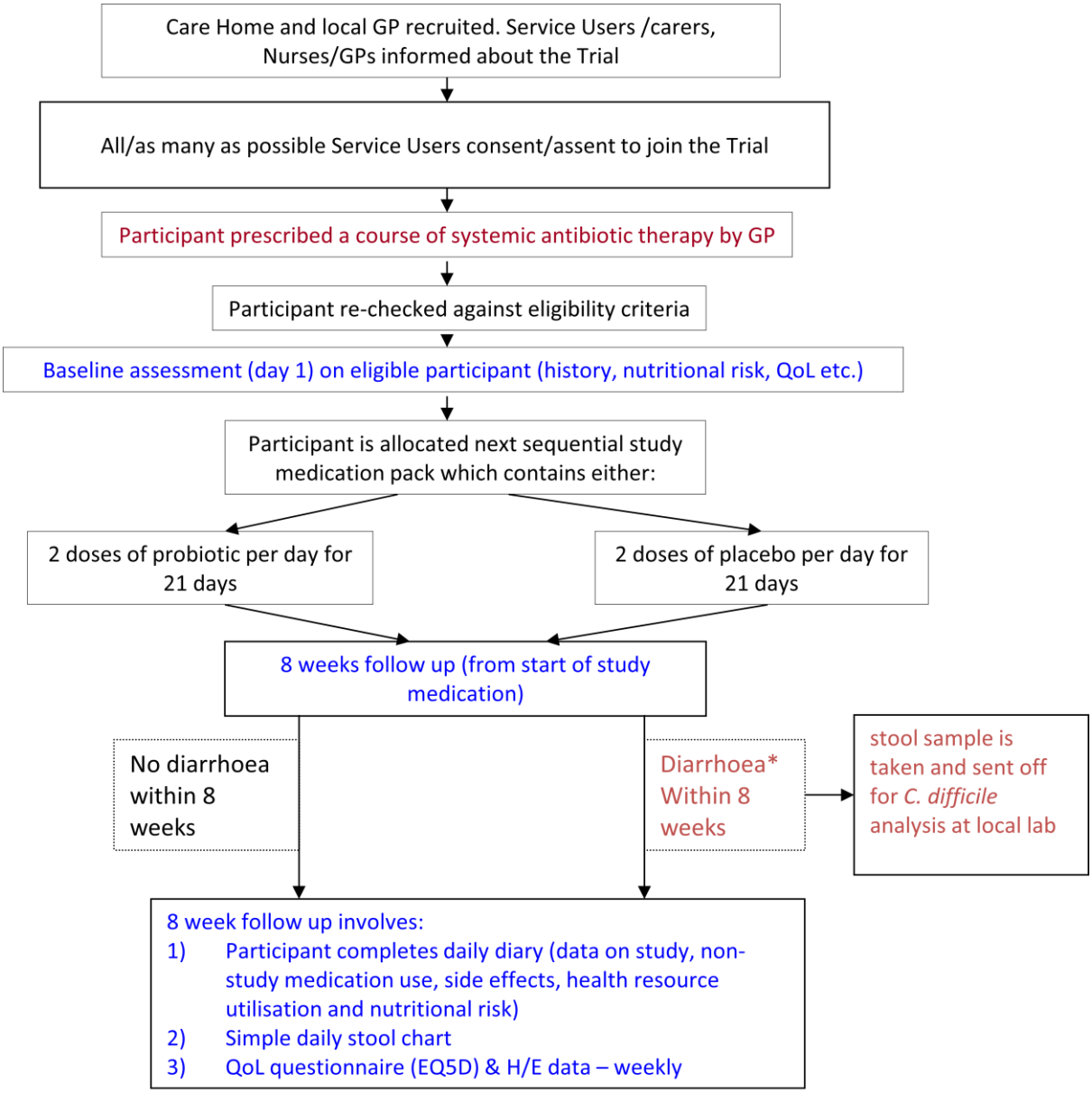


Figure 2. Participant flow diagram



4 Introduction

4.1 Background

4.1.1 Antibiotic Associated Diarrhoea (AAD)

Antibiotic treatment disrupts the normal flora of the gut, sometimes causing diarrhoea. While any antibiotic can cause AAD, clindamycin, cephalosporins, aminopenicillins and more recently fluoroquinolones, have been identified as more likely to cause AAD, particularly in hospitalised patients. Older patients with frequent hospitalisations and high co-morbidity are at greatest risk of developing AAD. Little is known either about the frequency and type of antibiotics prescribed in care homes in the UK and internationally, or about the incidence and aetiology of AAD in this setting. AAD varies in seasonal incidence being more common in winter, and has been shown to occur in up to 44% of hospitalised patients receiving antibiotics [1].

4.1.2 *Clostridium difficile* (*C. difficile*)

Clostridium difficile is a Gram-positive, spore-forming bacillus. It was first described in 1935 and by 1978 it had been identified as the pathogen responsible for pseudomembranous colitis[2]. It has more recently been highlighted as a potentially serious threat to hospitalised patients and care home SUs, causing high levels of morbidity and, in some cases, death [3,4]. The spores of *C. difficile* can survive for lengthy periods in the environment and gut; therefore, there is a high risk of cross infection, not only through direct patient-to-patient contact, via healthcare staff, but also via a contaminated environment. Routinely collected voluntary surveillance Health Protection Agency (HPA; www.hpa.org.uk) data (2009) show that though the incidence rate of *C. difficile* per population is decreasing since 2008, the incidence rate is still high in England Wales and Northern Ireland being 50, 59 and 55 samples per 100,000 population respectively. Around 77% of all reported cases were in the 65 years and over age group.

4.1.3 *C. difficile* associated diarrhoea (CDAD)

C. difficile associated diarrhoea (CDAD) is the most commonly identified cause of AAD, and most cases of pseudomembranous colitis. CDAD typically occurs in hospitals (including community hospitals) but also occurs in care homes and primary care settings (Department of Health; www.dh.gov.uk). CDAD occurs most often as a consequence of disruption of the indigenous colonic microflora following broad-spectrum antibiotic treatment. *C. difficile* accounts for 20-30% of AAD [5], although some estimates are more conservative [6]. In the majority of patients, full recovery is usual, although particularly elderly and frail patients may suffer loss of dignity, become seriously ill with

dehydration as a consequence of the diarrhoea, and may progress to develop life threatening pseudomembranous colitis.

Exposure to antibiotics within the previous two months is the most important risk factor for developing CDAD [7]. Other well-recognised risk factors include age (e.g. hospital patients aged over 65 years are four times more likely to develop CDAD compared to younger, general medicine patients: 73.6 vs. 16 per 1000 admissions), hospitalisation, severity of underlying illness, nasogastric tube and use of proton pump inhibitors or H_2 antagonists [8-10].

4.1.4 CDAD and AAD infection in care homes

There is limited data regarding antibiotic use, and incidence of AAD and CDAD in care homes. Most of the research to date has been carried out in hospital settings or in the US. However, SUs in care homes in the UK have many of the risk factors associated with developing AAD and CDAD (e.g. over 65 years, frail, multiple co-morbidities). Antibiotic use in US residential homes is common: estimations of single time-point prevalence ranges from 8% to 17%. Between 50% to 75% of SUs received at least one antibiotic prescription over a twelve-month period [7]. We conducted a prescribing audit of care homes in one Health Authority and found that 134 (7%) of 1901 SUs were on an antibiotic on a single day. A study in care homes in Sweden showed 25% of SUs were prescribed an antibiotic during a three month observation period.[11] Considerably fewer antibiotics are prescribed in Sweden compared to the UK.[12] It is not stated how many of these SUs developed AAD nor how many had *C. difficile*. Providing reasonable estimates of these outcomes for the UK is important to the NHS for the purposes of service planning and developing prevention strategies. Diarrhoea within long-term care facilities can cause considerable morbidity, fatalities and may become endemic. Up to 33% of patients in secondary care in the UK develop diarrhoea after antibiotic treatment. [12]

Laffan and colleagues retrospectively reviewed CDAD incidence and prevalence in a single 200 bed Long Term Care Facility (LTCF) in Baltimore in the US between July 2001 and December 2003. Incidence of CDAD ranged from 0 to 2.62 cases per 1000 resident days. They found that CDAD in this LTCF occurred most often in patients who had recently been admitted to hospital [13]. US studies by Kutty and colleagues and Chang and colleagues found that over 90% of post hospitalisation cases of CDAD occur within 30 days of discharge [14, 15]

Riggs and colleagues in the US found that over 50% of patients admitted to a LTCF during an outbreak were asymptomatic carriers of *C. difficile* (stool culture positive but no diarrhoea) [16].

4.1.5 What are probiotics and why might they prevent AAD and CDAD?

Probiotics are dietary supplements containing a mono or mixed culture of live microorganisms such as bacteria or yeasts, which, when administered in adequate amounts, confer a health benefit on the host by improving the properties of the indigenous microflora [17]. Although the bacterial preparation to be used in this study is not yet known to confer a health benefit in this context, the term "probiotic" will be used for simplicity. Probiotics have been suggested as an intervention for AAD, including *C. difficile*, as they reinforce the human intestinal barrier and help maintain the commensal gut flora [2, 18-20]. Antibiotics kill sensitive organisms in the gut, providing an opportunity for resistant organisms to flourish without competition from sensitive organisms. Probiotics might replace and occupy the niche formally occupied by the organisms killed by the antibiotics. Probiotics are resistant to digestion by enteric or pancreatic enzymes, gastric acid and bile, and are thought to prevent the adherence, establishment and/or replication of pathogens in the gastrointestinal tract. They also break down and consume substances (certain fatty acids) that could cause diarrhoea

A meta-analysis of 10 randomised, blinded placebo-controlled trials included 1862 paediatric and adult patients who received *Lactobacillus* as a single agent regimen or placebo to prevent AAD. The pooled relative risk ratio (RR) of developing AAD was significantly lower with *Lactobacillus* compared with placebo (RR 0.35, 95% confidence interval [CI] 0.19-0.67). In a subgroup analysis, this difference between groups is statistically significant for adults but not for children. This is likely to be due to the continuing efficacy of the probiotics in children. (RR 0.24, 95% CI 0.08-0.75 and RR 0.44, 95% CI 0.18 to 1.08, respectively)[21]

Probiotics may therefore be an attractive option for preventing AAD because they are inexpensive (the cost of preventing one case in highly selected hospitalised patients may be as low as £50)[22]. Although the prevention of AAD will provide a communal benefit not only to the CHS but also to the other SUs and the LTCF, these benefits are not measured.

4.1.6 Safety of Probiotics

Probiotics carry theoretical risks including infection beyond the gut, and transfer of antibiotic resistant genes. However, so far, there have been no reports of bacteraemia or fungaemia attributable to the probiotics in trials included in published systematic reviews. *Lactobacillus* bacteraemia is rare and has a low mortality rate [23]. In terms of conducting a RCT, cancer, diabetes, broad spectrum antibiotic therapy, organ transplantation, may also be risk factors. Septicaemia is very rare but may be a consequence of taking probiotic, while abscesses can also be a consequence. There have been 12 reported cases of *Lactobacillus* bacteraemia in patients taking a probiotic and 24

cases of fungaemia associated with the probiotic *Saccharomyces boulardii,* however this latter species of yeast is not an active species in the active probiotics VSL#3, used as the IMP in this study. However, many *Lactobacillus* strains are human commensals and a review identified only five well documented published cases where the consumed probiotic strain was the same as a clinical isolate.[23] Mild to moderate gastrointestinal side effects, such as flatulence and rash are generally no more common than in patients on placebo.

4.1.7 Conducting research in care homes

Conducting research studies in care homes, especially in nursing homes, poses unique challenges. Research participants resident in care homes are more likely to be older, more frail and more likely to be cognitively impaired compared to participants from most other research settings [24]. Recruitment, consent, retention and data collection can be time consuming and difficult and extra time and help will need to be provided to ensure that the staff in care homes have the support to carry out the research procedures [25]. Junior CHS turnover is frequent, though senior staff tend to remain in post long-term. Very little scientifically robust research has been conducted in care homes in the UK. Good practice and excellent care require robust underpinning research and an important and increasing part of our population are resident in care homes. Developing research methods for the care home sector is crucial to providing the best possible care for this population.

4.2 Rationale for current study

Surveillance data (incomplete) and UK clinical experience suggests that AAD, including CDAD, could be an important problem in UK care homes. In addition, there are strong grounds for evaluating probiotics in conjunction with antibiotic treatment to prevent AAD in care home SUs, but this has never been evaluated in a robust clinical trial. The age of this sample population, together with the multiple co-morbidities predisposes this sample population to infections, resulting in prescribed antibiotics. Treatment with antibiotics then predisposes this population to diarrhoea.

We have conducted an initial observational study (PAAD Stage 1) in preparation for this study (PAAD Stage 2). In order to assess the feasibility and establish the importance of the problem before proceeding to an RCT, an interim analysis was carried out on PAAD Stage 1 data in June 2011. This used pre-specified agreed stopping rules as the criteria for deciding whether to proceed to an RCT or not.

The purpose of the interim analysis in Stage 1 was to:

- Provide evidence of the importance of AAD in care homes;
- Provide a firm basis for a sample size calculation for Stage 2 RCT;
- Ascertain the practicalities of conducting an RCT in a care home setting.

Appendix 3 summarises the results from the interim analysis, comparing them with the stopping rules. In summary there were four outcome measures which were analysed at the interim analysis time point as stopping rules, to consider whether to proceed to the Stage II RCT. These were:

- **Recruitment-**
    - Greater than 60% of the total SUs approached should be recruited. We recruited 72% of eligible SUs at this time point.
- **Antibiotic prescribing-**
    - Greater than 27% of the recruited SUs should have been prescribed at least one course of antibiotics. The results show that 46% of the SUs received at least one course of antibiotics.
- **Incidence of AAD –**
    - Greater than 18% of the prescribed antibiotics should result in at least one episode of AAD. We found that 34% of the prescribed antibiotics with follow-up data resulted in at least one episode of AAD.
- **Severity of AAD –**
    - The proportion of antibiotic prescriptions resulting in at least one episode of AAD should be greater than 18% and the proportion of severe AAD episodes (defined as AAD lasting longer than two weeks, AAD resulting in hospitalisation or death or AAD attributable to *C. difficile*) should be low. The results show that there were no episodes of AAD lasting longer than two weeks, while of the 34 diarrhoeal stool samples that had been analysed, 24% were found to contain cultures of *C. difficile.* Furthermore, there were no episodes of AAD that resulted in hospitalisation or death.

The estimates obtained from the interim analysis exceeded all of the pre-defined stopping rules and established that proceeding to an RCT was both feasible and important.

4.2.1 Sub-Studies

To account for gaps in the evidence and to properly plan the trial outlined for Stage II, and the anticipated difficulties in trial implementation, two sub studies have been

conducted within PAAD Stage 1. The sub-studies have provided information on the incidence of asymptomatic *C. difficile* in care homes and methods for improving study/clinical trial management procedures within care homes.

4.2.2 Prevalence of *C. difficile* Sub-Study

This study was carried out to establish the rate of asymptomatic carriage of *C. difficile* in care home SUs and was an optional consenting component for all SUs.

The antibiotic prescribing data for the three months prior to consenting for each SU taking part in the study was also collected. This data provided valuable research information for comparison with the antimicrobial sensitivities of bacterial isolates identified in baseline stool samples.

Since the Stage 1 study is currently on-going, the final results of this Sub-study are currently unavailable.

4.2.3 Qualitative Sub-Study on consent procedure options

A qualitative study was carried out to establish the feasibility and acceptability of taking advanced consent/assent for research trial procedures in care home SUs to broaden our understanding of consent/assent issues in this vulnerable population, and to inform the development and training materials for CHS in how to conduct the RCT.

The qualitative study incorporated focus groups and individual interviews with CHS, and interviews with SUs, family members, and GPs.

4.2.3.1 GP Interviews

Nine GPs were interviewed. No major ethical or safety concerns were raised by them regarding PAAD Stage 1 or 2. Indeed, respondents regarded the study as having great potential to benefit SUs. GPs recommended that:

- SUs or their personal legal representatives do not need to be re-consented at regular intervals during the 12 months of PAAD Stage 2. However, they should be kept informed of the PAAD study through the care home regular briefings and that SUs with capacity are reminded at the point of randomisation that they have consented to participate in the PAAD Study. The personal legal representatives should be reminded that the SU has been randomised for PAAD Stage 2 when the CHS inform them that SUs have been prescribed antibiotics.
- In the event that a SU loses capacity during the study period, then their relatives can be informed but the SU should continue on the study.

- That the eligibility assessment and authorisation of the Investigational Medicinal Product (IMP) are kept as streamlined as possible, with some of the paperwork completed by RNs.
- That the research team consider the ethical implications of paying GPs for assessing eligibility and authorising the IMP, and ensure an adequate justification is provided to the main REC.
- SUs should only be randomised by GPs in the community, including out of hours doctor, but not by a dental practitioner or a hospital doctor.
- That the PAAD study team consider putting a package together to encourage GPs to participate in the PAAD Study which includes elements of Continuous Professional Development, financial incentives, and practice based analysis.

4.2.3.2 Relative/Consultee Interviews

Out of the fourteen relatives interviewed, all were eager for their SU relative to take part in the PAAD Stage 2 study and were happy for the consent to apply for 12 months. Many relatives stated that they recognised that nutritional supplements, as an intervention, were not dangerous and that there were many potential benefits to medicine and society. No major ethical concerns were spontaneously raised by relatives. Relatives made it clear that:

- The study information sheet should be simple and short, rather than being overwhelmed with paperwork. The information should ensure that the SU was eligible to enter the study if they need antibiotics.
- Some relatives did not think that SUs should need to be re-consented in the event that antibiotics were prescribed and the patient randomised; while some did consider it best to check whether SUs with capacity or their relatives are willing to continue on the study at regular intervals. However, they considered that such checking would not need to be established in writing.
- Ensure the information clearly states that if the SU loses capacity during the study, then their relative will be informed of their participation in the study as a courtesy only.

4.2.3.3 Care home staff Interviews

Two focus groups were conducted with CHS (one with managers/matrons and one with more junior staff) totalling 16 CHS. In addition, we conducted four additional one-to-one interviews with CHS that were unable to attend the focus groups.

CHS were generally very positive about the value of the PAAD Study and their participation in the study. They reported that their original willingness to participate in

PAAD arose from a belief that older people were generally neglected in research, that antibiotics and diarrhoea were important issues to be addressed for this client group, that there were professional benefits for staff through increased training and links to Cardiff University, and a sense that they were providing benefit to society. However, having started the PAAD Study most CHS were surprised at the intensity and the scale of the paperwork involved.

The salient points raised by the CHS were:

- Communication between staff was an issue. Information about the PAAD Study was not always appropriately cascaded down to junior staff and care homes took different approaches to reminding staff about PAAD.
- That the CHS should be appropriately trained as to what should happen should a SU lose capacity, and relatives are told that they are being informed as a matter of courtesy. Failure to establish a protocol for this arrangement is likely to lead to differing actions depending on the nature of the relationship between CHS and relatives.
- That care homes develop systems to communicate with SUs and relatives about the continued participation of the care home in the PAAD Study (through newsletters, posters, relatives meetings etc), and that relatives are reminded at the point of randomisation that the SU is participating within the study. Additional written consents throughout the year are not required.
- That clear guidance is provided to CHS as to the meaning of a 'personal legal representative' and that the PAAD Protocol details the actions to be taken should a personal legal representative die or lose capacity.
- That care homes demonstrate that they are using the Bristol Stool Chart (BSC) within the care home before they are recruited into the study.

All of these recommendations have been included as part of this RCT protocol, including practical implications, e.g. taking consent, and developing a training package for care home study sites.

5 Study objectives

5.1 Primary objectives

- To compare the effectiveness of probiotics vs. placebo, taken in conjunction with antibiotics, on the incidence of AAD in care home SUs.

5.2 Secondary objectives

- To compare the effectiveness of probiotics vs. placebo, taken in conjunction with antibiotics, on the duration and severity of AAD in care home SUs.
- To compare the effectiveness of the probiotics vs. placebo in reducing the incidence of *C. difficile*–associated diarrhoea (CDAD) in care home SUs.
- To evaluate *th*e impact of the probiotics on Quality of Life (QoL) in care home SUs.
- To evaluate the cost effectiveness of probiotics for AAD in care home SUs.

6 Study design

This is a phase III individually randomised, double-blinded, parallel group trial of probiotic versus placebo for care home SUs who are prescribed antibiotics for acute infection. A total of 400 SUs from approximately 24 care homes in Wales (and potentially England) will be randomised.

The target population are SUs resident in care homes under a long-term care plan. Data entry, management and analysis will be conducted centrally at the South East Wales Trials Unit (SEWTU).

7 Centre and Investigator selection

Care homes located in Wales and if necessary from the South West and other parts of England will be approached to take part in the PAAD Study. We will seek agreement about participation in the study from the manager and the owner of suitable care homes. An agreement, detailing roles and responsibilities will be signed by the care home manager and the owner of the care home. The care home manager will be defined as the Principal Investigator (PI) at the care home, as the study site, and by Cardiff University as the sponsor of the study.

7.1 Recruitment of Care Homes

We will aim to recruit large care homes with a minimum of 50 SUs in order to organise and plan recruitment. Care homes with less than 50 SUs may be selected if they have adequate recruitment potential. Each care home will need to have at least three interested staff to take responsibility for conducting the study in their care home, with all appropriate (i.e. at least one senior) members of staff certified in ICH GCP training.

From a list of care homes within Wales in the first instance, care home managers will be approached and asked to give permission for their care home to participate in the study. The care home manager will seek permission from the care home private owner, or their local authority, which shall be sought in writing before an agreement is set-up with the care home.

Before any care home can begin recruitment a PI at each care home must be identified and it is the responsibility of the PI to ensure the following documents are received by the PAAD stage 2 RCT Trial Manager (TM) (see contact details on page 6):

- SSA Approval
- SSI approval (where required)
- A signed Trial Agreement (PI and sponsor signature);
- Completed Signature List and Roles and Responsibilities document;
- Completed contacts list of all site personnel working on the Study;
- Consent forms and SIS (including verbal) for SUs or legal representatives on care home letter headed paper;
- Confirmation that the lead GP (or delegates) associated with the care home is (are) willing to be involved

Study sites will not be open to recruitment and must not recruit participants until they have received a letter from the TM confirming that they can start recruiting. Upon receipt of all the above documents and confirmation from the MHRA that the Centre and PI has been added to the PAAD stage 2 RCT CTA, the PAAD stage 2 RCT Trial Manager will send a confirmation letter to the PI/lead RN at site, detailing that the centre is now ready to recruit SUs into the study. This letter must be filed in each care home Site File.

Along with this confirmation letter, the care home should receive their study supplies and a trial pack holding all the documents required to recruit SUs into the PAAD Stage 2 RCT.

8 Participant selection

SUs are eligible for the study if they meet all of the following inclusion criteria and none of the exclusion criteria. All queries about SU eligibility should be directed to the PAAD stage 2 RCT Trial Manager before enrolment, recruitment or randomisation.

8.1 Inclusion criteria at consent

- Resident in a care home for 24 hours or more, with a minimum planned period of residential care of 1 month.
- Able to provide informed consent or have a personal legal representative who can provide consent for inclusion.
- If the SU takes a regular probiotic but chooses to discontinue the probiotic

8.2 Exclusion criteria

- Severely immuno-compromised, e.g. known severe neutropenia
- Has artificial heart valve in situ.
- Medical history of acute pancreatitis.
- Requires naso-jejunal feeding /nasogastric feeding Currently has a colostomy.
- SU without capacity already receiving a probiotic

9 Recruitment and randomisation of Service Users

Following site initiation, the care home will aim to enrol all eligible SUs at that site. At this point, SUs (or their representatives) will be asked to provide consent to be monitored for up to one year and to be randomised to receive probiotic or placebo should they be prescribed antibiotics for acute infection in the course of routine care during this period.

There are likely to be two types of SUs who are eligible to join the study; those who have capacity and are able to consent for themselves and those unable to consent for themselves (lack capacity). Consent procedures will differ according to the mental capacity of the SU. ICH GCP trained senior care home staff/care home nursing staff or trained PAAD study RNs, will be responsible for consenting SUs or their personal/professional legal representatives.

9.1 Mental Capacity Assessment

Mental capacity will be assessed according to the Mental Capacity Act 2005, which provides a legal framework within which health and care professionals must act. As such all care homes have senior staff members who are fully trained to assess the mental

capacity of SUs at any time. This Code of Practice provides comprehensive advice on good practice for the assessment of capacity, and depends on clinical judgement within a valid contestable process.

According to the Mental Capacity Act, the SUs will be presumed to have capacity, unless there is any reason to doubt their mental capacity. In the event that there is any doubt raised by the care home staff or the researchers, the SU will be assessed for mental capacity by the PAAD senior RN or the senior care home staff. A standard template for recording of the mental capacity assessment will be provided to care homes, together with specific training on the use of this template to the senior care home staff. This document will be reviewed by the PAAD RNs or senior care home staff to enable a decision to be made regarding the mental capacity of the SU, prior to taking consent from the SU or their legal representatives.

9.2 Cooling- Off period

During the recruitment period of PAAD Study Stage 1, the care homes as study sites reported that relatives/consultees wished to sign the "consultee declaration of assent form" on the day that they were provided with the information about the study. Some relatives did not wish to wait for 48 hours before making a decision, as they felt they had considered all the issues, had access to sufficient information and all their questions had already been answered. Many visited the care home infrequently, and so a period of enforced delay would limit the SU's opportunity to participate in research. Enforcing a pre-determined 'cooling off' period, irrespective of the time required by the person providing consent/assent for this study was considered patronising by many relatives. They preferred to be able to provide consent/assent at the point they felt ready to do so.

The Information Sheet for personal/legal representatives can be sent by post, however a face-to-face discussion for informing the relative is the method of choice in many care homes. Furthermore due to the type of IMP under investigation (Type B according to the risk adapted approach to conducting IMP trials), it was considered that for SUs with full capacity and legal representatives of SUs without full capacity should be given as much time as they require. This period of time could mean providing consent on the same day or after as much time as required to obtain informed consent.

9.3 Number of participants

In order to reach our target of 400 randomised service users, we estimate 1214 SUs will need to be approached to take part in the PAAD study and 607 SUs will need to be recruited to the enrolment stage by obtaining advanced consent.

9.4 Recruitment process

There are two stages to recruiting SUs to the study:

The first stage is the enrolment stage (see section 9.5). All eligible SUs in care homes can enrol and provide consent to take part in the study. CHS, nursing staff, PAAD Study RNs or the Research Officers (ROs), who are trained to take consent, will identify those SUs who are potentially eligible to join the study. There will be two types of participants within this study those with capacity (see section 9.5.1) and those without capacity (9.5.2) and the recruitment process will differ accordingly.

The second stage is the randomisation stage (see section 9.6), which occurs when an enrolled SU is prescribed an oral antibiotic. At this stage, the GP will re-assess the SU to ensure that they still meet all of the eligibility criteria.

9.5 Informed consent

Informed consent must be taken by suitably qualified, experienced and trained personnel in accordance to the ICH GCP directive on taking consent and before any study related procedures are undertaken. Written informed consent will be obtained from the SU or their personal (a person not connected with the conduct of the study, who is suitable to act as the legal representative by virtue of their relationship with the adult and available and willing to do so, i.e. next of kin, those who visit most regularly)/professional (a person not connected with the conduct of the study who is: (a) the doctor primarily responsible for the adult's medical treatment, or (b) a person nominated by the relevant health care provider (e.g. an acute NHS Trust or Health Board)) legal representative.

Prior to consenting to take part in the study, all SUs or their personal legal representatives, will be notified that they can withdraw their consent at any time during the study period. The SU/representative will be allowed as much time as needed to consider the information, and the opportunity to question the CHS, study RNs, ROs, their GP or other independent parties to decide whether they will participate in the study.

The following information sheets and consent forms will be provided to the care homes:

Service user

1) SU information sheet (SIS)
2) SU user consent form

Service user's representative

1) Detailed personal /professional legal representative information sheet

2) Personal / professional legal representative consent form

1) Verbal Consent Form for SUs or personal/professional legal representatives

In the event that a SU requires a more accessible information sheet this will be provided using either:-

a) a simplified pictorial version of the study information sheet interpretation by sign language for the hard of hearing
b) translation of the information into Welsh or an ethnic minority language

9.5.1 SU with Mental Capacity

According to the Mental Capacity Act, all SUs will be presumed to have capacity, unless there is any reason to doubt their mental capacity. If the SU has capacity, the person taking consent will provide the SU with written and verbal information about the study, ensuring that the information is fully understood. Understanding and consent will be checked by asking the SU to repeat back important aspects of the study. If they are happy to participate, SUs with capacity will be asked to sign and date the consent form, which will be countersigned and dated by the senior care home staff/nursing staff or RN taking consent. A copy of the signed Informed Consent form will be given to the SU and the original signed form will be retained at the study site. The SU's GP will be informed that they are taking part in the study.

9.5.2 SU without mental capacity

If the person taking consent makes the assessment that the SU lacks mental capacity, a standard template for recording of the mental capacity assessment will be completed. They will then liaise with the senior care home staff or nursing staff to identify a personal legal representative. In the event that a personal legal representative cannot be contacted by telephone or are themselves without capacity, the SU's professional legal representative will be contacted for consent. The SU's professional legal representative must not be the SU's own GP, if that GP is involved in the running or management of the care home.

The SU's personal/professional legal representative will be provided with information about the study and will be asked whether or not the SU would want to join the study. The personal/professional legal representative will then be asked to provide consent on

behalf of the SU to join the study. The care home staff will inform any other relevant persons who need to be informed, e.g. SU's Social Worker or Case Manager, i.e. traditional professional social carers, as currently defined within social care. If they are happy for their relative (the SU) to participate, they will be asked to sign and date the consent form, which will be countersigned and dated by the senior care home staff/nursing staff or RN taking consent. A copy of the signed Informed Consent form will be given to the personal/professional legal representative and the original signed form will be retained at the study site. Since some personal legal representatives may not be able to attend a face-to-face interview for the consenting procedure, these documents may be sent by post from the care homes. The care home senior staff/RN or ROs will countersign signed and dated consents returned by the personal/professional legal representatives and a copy of the completed consent form will be sent to the personal/professional legal representative. The original consent document will be retained at the study site.

If the personal/professional legal representative wishes to provide consent immediately after receiving the information sheet on the study, they will be able to do so. All legal representatives who have not responded will be contacted by phone at least once by the CHS, the study RN or by ROs.

In the event that a personal/professional legal representative themselves loses capacity or dies during the study period, an alternative personal/professional legal representative will be contacted. If there is no one to represent the SU in the study, the SU will be excluded.

If the SU's own GP is the designated professional legal representative, an alternate GP within the same general practice, who is not involved in the conduct of the study, or the running or management of the care home, will be asked to act as their professional legal representative.

9.5.3 Verbal consent

In the event that a SU with capacity or a legal representative for a SU without capacity cannot provide handwritten signatures on the consent document, a verbal consent will be taken. In such cases, one of the senior CHS will read and discuss the study with the SU or their legal representative to ensure understanding of the study protocol. A member of the Research Team will witness, sign and date the consent document to approve that consent has been given.

9.6 Randomisation and unblinding

Randomisation will be coordinated centrally by SEWTU. The trial statistician will produce the main randomisation list. SEWTU will provide SMPU with a list of random allocations numbers linked to either placebo or probiotic, which will be used to label the study medication packs. Each medication pack will be labelled with a unique identification number (study medication pack number). This study is a double blind trial therefore, the SUs, consultees, care home staff nor the PAAD study team will be aware of the treatment allocation. The unique identification number on each study medication pack will be linked to the randomisation file, which will only be accessible by the trial statistician.

9.6.1 Allocation of Study Medication

Once an antibiotic for an acute infection has been prescribed to a SU who has provided advanced consent to participate in the study, the SU will be re-assessed against the following exclusion criteria. All criteria must be answered no for a SU to be allocated study medication (i.e. randomised)

Exclusion criteria

- Previously been allocated study medication
- Service User's stool pattern is diarrhoea (defined as 3 or more stools at BSC type 5-7 within 24 hours)
- Severely immuno-compromised, e.g. known severe neutropenia
- Has artificial heart valve in situ.
- Medical history of acute pancreatitis.
- Requires naso-jejunal feeding /nasogastric
- Currently has a colostomy.
- SU is taking a probiotic on a regular basis and is unwilling to discontinue use.

General Practitioners (GPs), visiting their SU, will assess the SU for Eligibility for Study Medication CRF to re-confirm their eligibility at the same time as they prescribe the antibiotic(s). In the event that re-confirmation of eligibility and randomisation authorisation has not been obtained at the time of GP visit, the CHS will be trained and encouraged to alert the researchers by telephone or by fax within 24 hours of the SU being issued with a prescription. The RNs may assess eligibility; however the final approval for randomisation of the SU will be from a responsible clinician at the SU's general practice obtained either by fax from the RN or by a personal visit by a researcher to the GP surgery.

When the SU has been confirmed as eligible, the next sequentially numbered study medication pack will be allocated to the SU.

In the event that the researchers cannot obtain GP approval for randomisation and prescription completion for the study medication within 72h, the SU will be monitored until such time they are prescribed a further antibiotic. At this time point the same procedure as described above will be followed.

9.6.2 Unblinding participants.

In the event that the SU needs to be unblinded the care home staff are directed to contact the PAAD team on 02920 687541. The PAAD unblinding SOP will be followed to un-blind the participant and in this case the un-blinding of randomised SUs can only be carried out by the QA Manager at SEWTU.

9.7 Screening, enrolment and randomisation logs

A screening, enrolment and randomisation log will be prepared for each care home and will be populated from the care home list of current residents. The log will record when SU are approached, whether they were consented and subsequently randomised and any reasons for a SU being excluded, not consenting or not being randomised. This information will be recorded so that any bias from differential recruitment can be detected. An anonymised screening log will be faxed or a photocopy sent to the PAAD TM at regular intervals to allow monitoring of recruitment progression.

10 Withdrawal & loss to follow-up

10.1 Withdrawal

SUs may withdraw consent for participation from any aspect of the study at any time. The care of SUs will not be affected by declining to participate or withdrawing from the study.

If the SU does not have capacity to consent, their personal/professional legal representative may withdraw them from any aspect of the study at any time, without their future clinical care being affected. The Investigator or the SU's GP may withdraw SUs from the study intervention at any time if he/she considers that the SUs health or

wellbeing is compromised by remaining in the study. The CHS/PAAD research nurse will notify SEWTU of the withdrawal of the SU by telephone as soon as possible, and arrangements made for the withdrawal form to be sent via fax (if possible). The TM will liaise with the CHS/PAAD research nurse to obtain the hard copy of the form at the next available opportunity.

A withdrawal CRF will be completed either:

- When a SU expresses their desire to withdraw from the study;
- When a SUs personal/professional legal representative expresses their desire for the SU to be withdrawn from the study.

Furthermore, if a SU initially consents but subsequently withdraws from the study the SU will be asked to decide whether they would:

- wish to withdraw from the study, but allow the data to be collected until the end of the study
- wish to withdraw from the study, but refuse to allow data to be collected until the end of the study
- wish to withdraw from study and require all data collected to date to be destroyed

A SU may withdraw or be withdrawn from the study intervention by the Investigator for the following reasons:

- Any alteration in the participants condition which justifies the discontinuation of the study intervention in the Investigator's opinion,
- Intolerance to the study medication.

10.2 Loss to Follow-up

Care home staff will be requested to notify the PAAD trial manager of any participant who moves out of their care home during the 8 week follow up period.

11 Study Intervention

There are two intervention arms on the PAAD Study Stage 2 RCT. The active arm is the nutritional supplement VSL#3 probiotic which contains approximately 450 billion live lactic acid bacteria and bifidobacteria, together with maltose and silicone dioxide. There are eight different strains of potentially beneficial bacteria: *Streptococcus thermophilus, Bifidobacterium breve, Bifidobacterium longum, Bifidobacterium infantis, Lactobacillus acidophilus, Lactobacillus plantarum, Lactobacillus paracasei and Lactobacillus delbrueckii subsp. Bulgaricus*.

The matching Placebo arm of the study consists of (4.4g) of freeze dried powder 4.4g, matched for taste, consistency, odour and colour. The use of an indistinguishable placebo will avoid the biasing of identification and assessment of outcomes.

11.1 Dispensing Study medication

SUs who have provided advanced consent, have been prescribed antibiotic(s) and remain eligible for study medication, will be randomised to receive either the active probiotic or the placebo. At this point, the SU will be allocated study medication (see 9.6.1 for details on allocation of study medication). Study medication should commence ideally on the day the antibiotic was started, and no later than 72 hours after.

The SU should be given one sachet twice a day. The sachet should be opened and the contents stirred into cold water or any non-fizzy drink or cold food and consumed immediately. The study medication should be given in between the antibiotic therapy and not in conjunction with the antibiotic.

Accidental contamination with small numbers of the probiotic bacteria by participants allocated to the placebo arm due to the probiotic being prepared in the same environment may occur; however the level of airborne contamination is likely to be minimal. A designated area for the dispensing and preparation of the study medication, will be discussed with each care home while all staff will be guided in preparation and administration of the study interventions to minimise cross-contamination. Plastic pots (if required) will be provided to reconstitute the study preparation before consumption.

11.2 Supply, packaging and reconciliation of study materials

Primary bulk manufacturing, labelling and delivery of both VSL# 3 and placebo will be performed by Actial Farmaceutica Lda, Portugal. Actiel, will grant the licence of use of these products in the UK and also provide primary Qualified Person (QP), release. Bulk batches will be delivered to St Mary's Pharmaceutical Unit (SMPU), which is a pharmaceutical

manufacturing facility and part of the Cardiff and Vale University Health Board and stored according to manufacture conditions.

SMPU will label and pack individual intervention medication packs. Study medication will be packed into primary and secondary packaging. Firstly each individual sachet, (primary pack), containing probiotic or placebo, will be labelled stating 4.4g VSL$^{\#}$3 or matching placebo, for single use. The label will state 'for clinical trial use only', and designed in accordance with annex 13.

Sachet will be then be packed and sealed inside a card board box, (secondary pack), which again will be labelled according to annex 13 and will include enough study medication for a course for one participant.

An initial starter pack will be sent to care homes, which will consist of 6 study medication packs. Each medication pack will consist of 46 sachets enough for 21 days of study medication along with 4 extra to be used in case of spillage in preparation. Thereafter when the care home study medication levels reach 3 study mediation packs remaining, a PAAD Study Medication Requisition Form (requesting 6 study medication packs) will be completed and sent to the PAAD Trial Manager. Upon receipt of a PAAD Study Medication Requisition Form, the PAAD team will fax to SMPU who will arrange for a courier who will deliver 6 study medication packs via cold storage conditions within 48 hours.

The SmPC for VSL#3 states that the product should be stored in a refrigerator (2-8°C), therefore, upon receipt of study medication by the CHS, the PAAD reconciliation form will be updated and all study medication will be either stored in a PAAD designated fridge or within a designated area of an existing fridge within the care home. The temperature of this fridge will be regularly monitored using minimum/maximum calibrated temperature probe by designated CHS/RN. CHS will maintain temperature monitoring logs.

All unused sachets of the study medication (not included within the viability testing – see section 11.7) will also be disposed off according to local care home procedures and logged within the reconciliation form.

11.3 Dose modification for toxicity

If bloating is experienced, it is recommended to reduce the daily intake to half to allow for adjustment. If the participant continues to be uncomfortable the study medication should be stopped.

11.4 Pre-medication

There are no listed pre-medication for VSL#3.

11.5 Interaction with other medications

VSL#3 is believed to be compatible with all types of medications.

11.6 Permitted concomitant medications

All concomitant medications are permitted.

11.7 Viability testing

Randomly selected used opened packs of unused sachets from study preparation packs will be sent refrigerated to central laboratory for quality control check to confirm that the total number of live microorganisms is consistent with that stated in the certificate of analysis by the manufacturer, (450 billion lactic acid bacteria and *bifidobacteria*). However, given the existing quality control procedures for the manufacture of this product, identification of the individual bacterial strains contained in VSL$^{\#}$3 will not be undertaken. Similarly the placebo sachets will be tested to confirm the absence of active microorganisms.

12 Pharmacovigilance

12.1 Definitions

The following definitions are in accordance with both the Medicines for Human Use (Clinical Trials) Regulations 2004 (SI2004/1031) and the subsequent amendment regulations (SI2006/1938) and ICH-GCP:

Adverse Event (AE): Any untoward medical occurrence in a clinical trial participant to whom an IMP has been administered and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavourable and unintended sign (including abnormal laboratory finding), symptom, or disease.

Adverse Reaction (AR):

Any noxious and unintended response in a clinical trial participant to whom an IMP has been administered, which is related to any dose administered. A "response" to a medicinal product means that a causal relationship between a medicinal product and an adverse event is at least a reasonable possibility, i.e. the relationship cannot be ruled out.

Serious Adverse Event (SAE): Any adverse event that:

- Results in death,
- Is life-threatening,*
- Required hospitalisation or prolongation of existing hospitalisation,**
- Results in persistent or significant disability or incapacity,
- Consists of a congenital anomaly or birth defect,
- Other medically important condition, as assessed by the GP or the CI/delegated Safety Reviewer,***

* *Note*: The term "life-threatening" in the definition of serious refers to an event in which the participant was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.

** *Note*: Hospitalisation is defined as an inpatient admission, regardless of the length of stay, even if the hospitalisation is a precautionary measure, for continued observation. Pre-planned hospitalisation e.g. for pre-existing conditions which have not worsened or elective procedures does not constitute an AE.

*** *Note*: other events that may not result in death are not life-threatening, or do not require hospitalisation may be considered as a SAE when, based upon appropriate medical judgement, the event may jeopardise the participant and may require medical or surgical intervention to prevent one of the outcomes listed above.

Serious Adverse Reactions (SARs): A SAR is defined as any "reaction" occurring in a clinical trial participant for which there is a reasonable possibility that it is related to the IMP at any dose administered.

Suspected Unexpected Serious Adverse Reactions (SUSAR): These are **SARs** which are classified as 'unexpected' i.e. an adverse reaction, the nature and severity of which is not consistent with the applicable product information for VSL#3 probiotic.

12.2 Reporting procedures

All serious adverse events should be reported following randomisation up until the end of the eight week follow-up period. Depending on the nature of the event, the reporting procedures outlined in this protocol should be followed. Any queries concerning serious adverse event reporting should be directed to the study coordination centre in the first instance. A flowchart (Figure 2) is given below to illustrate reporting procedures.

12.2.1 Non serious AR/AEs

Since the study intervention is defined as a probiotic, which is a nutritional supplement, containing known species of live bacteria that are included in foods and commercially available, we do not request all adverse events (AEs) be reported. All expected adverse reactions will be recorded using the symptoms (Illness severity and symptoms CRF) section in the Daily Diary.

12.2.2 SAEs

All SAEs and reactions must be reported immediately by the care home manager or a senior staff member to SEWTU. A completed SAE form for all events should be faxed to SEWTU within 24 hours of knowledge of the event (or the next working day) on 02920 687612. A flowchart is provided in Figure 3 to aid in the reporting procedures.

Responsibility for the reporting of SUSARs and other SARs to the regulatory authorities (MHRA) and the REC are as follows:

- SUSARs which are fatal or life-threatening must be reported not later than 7 days after the sponsor is first aware of the reaction. Any additional relevant information must be reported within a further 8 days.
- SUSARs that are not fatal or life-threatening must be reported within 15 days of the sponsor first becoming aware of the reaction.

SAEs will be reported from the time a participant is randomised onto the study and for the 8 weeks follow up duration.

SAEs will be followed up by the PAAD team until they are resolved or the investigator assesses them as chronic or stable. The follow up and outcome of SAEs will be document in the appropriate CRF.

A list of all SARs (expected and unexpected) must be reported annually to the MHRA and REC.

12.2.3 SAEs

Due to the agreement between SEWTU and VSL/Actiel, all SAEs will be reported to the manufacturer of VSL$^{\#}$3.

Contact details for reporting SAEs

For the attention of the PAAD TRIAL MANAGER

Please Fax SAE forms to: 02920687612

Tel: 02920 687606 (Mon to Fri 09.00 – 17.00)

The SEWTU Standard Operating Procedure (SOP) for reporting any Serious Adverse Events (SAEs)) will be used to report to the sponsor, MHRA and Research Ethics Committee (REC).

12.3 Evaluation of SAEs

The principle investigator should ensure that all SAEs known to the care home staff are identified and each one assessed for causality and reported to SEWTU immediately as described in Figure 2. They will be evaluated by staff at SEWTU and one of the chief investigators (or their delegate) for seriousness, expectedness and causality. Investigator reports of SUSARs will be reviewed immediately and those that are SUSARs identified and reported to the regulator authority. In the event of a disagreement between the PI and CI regarding causality of an SAE, the highest relationship (i.e that closer to definitely related) will be reported. Expectedness of an SAE should be assessed in relation to the known adverse reactions described in the product characteristics for VSL$^{\#}$3 or the placebo provided by VSL/Actiel. Expected adverse reactions with the study interventions are listed below:

- excessive flatulence,
- bloating,
- skin rashes,

Please note: Although the information provided in the above table was comprehensive at the time the current protocol version was produced, the list of side effects may have been subsequently updated and the site staff /investigator should refer to an up to date SmPC.

12.4 Assessment of intensity

The intensity of all SAEs should be assessed by the PI according to the following definitions:

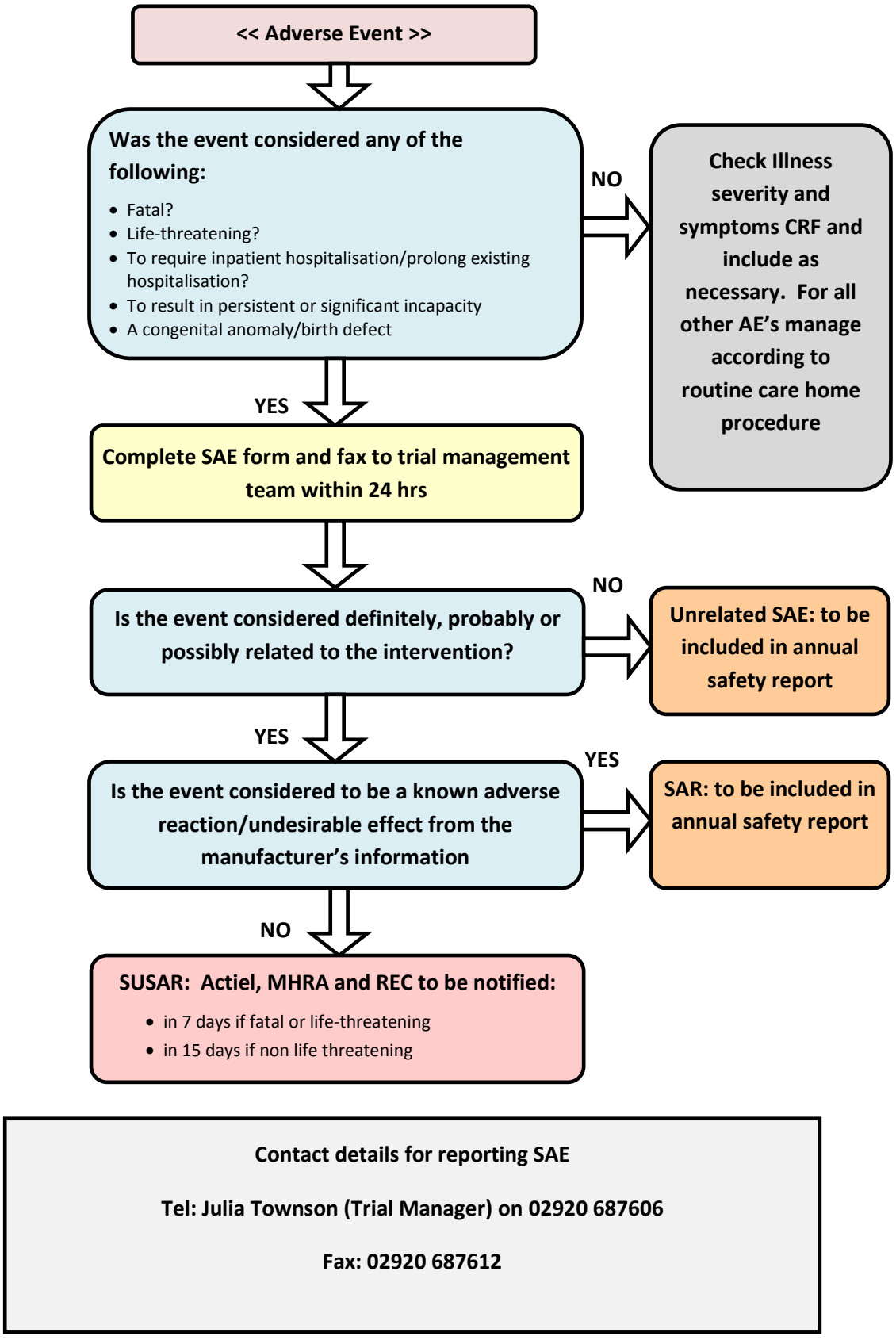
Mild – Does not interfere with SUs usual function
Moderate – Interferes to some extent with SUs usual function
Severe – Interferes significantly with SUs usual function

It should be noted that the severity and seriousness of an SAE are not the same classification, such that an SAE classified as severe (for example a headache) is not necessarily an SAE (unless it also meets the definition of an SAE in Section 7.2):

12.5 Causality

Causality of every SAE should be assessed using clinical judgement based on the information available to determine the relationship between the SAE and the intervention received by the participant. For the purpose of this trial, relationships will be classified as one of the following: not related; unlikely to be related; possible related; probably related; definitely related.

Figure 3 - Flow chart for Adverse Event Reporting Procedures



13 Study procedures

13.1 Training of staff

Training materials will be designed from the training plan used during PAAD Stage 1 and feedback from Sub-Study 3 (see above), where the views of CHS were established about necessary staff training.

The training schedule for staff will be tailored to meet the needs required by each individual study site. The training package will be designed specifically to train different staff groups, depending on the roles and responsibilities of the staff, e.g. Health Care Workers (HCWs) will be trained specifically on tasks of stool sampling, handling, storage and posting, but overall responsibility of delivering this task will remain with the senior care home staff. Designated staff members will have the responsibility of cascading training and delegating specific protocol tasks to other study site staff. Depending on the individual circumstances of the care home, the most appropriate members (i.e.at least one senior member of staff) will receive ICH GCP training and certification prior to commencement of SU recruitment. This member of staff will also have received training in the assessment of mental capacity. Taking informed consent will be carried out by ICH GCP trained senior CHS and RNs, however all CHS with designated roles and responsibility on the PAAD Study will be encouraged to receive ICH GCP training.

For the handling of the study medication designated dispensing staff at the care home will be provided with training at the start of the study, while further training will be provided by the researchers on an on-going basis as required by CHS. Emphasis will be placed on the use of designated cold storage (including temperature monitoring) of the study medication and recording of their administration and reconciliation for each SU randomised. Training will be provided for the maintenance of the level of stock of the study medication at the care home, which will be monitored by the researchers to ensure adequate supply.

13.2 Training of GPs and Responsible Clinicians

A GP at each practice linked to participating care homes will be selected as a champion of the PAAD Study. These champions will be asked to liaise with other GPs in the practice, any responsible clinicians, and the out of hours service providing GMS for the practice during evenings, weekends and bank holidays.

Each champion will receive training on the PAAD Study, including assessment of eligibility and authorisation of the probiotic/placebo in the event of an antibiotic being prescribed.
GPs will be reimbursed for their time spent on the PAAD Study.

13.3 Data collection/assessment

Table 1 details the PAAD Case Report Forms (CRFs) and questionnaires, time points for data collection and who has overall responsibility for collecting the data. Training for completion of trial CRFs will be provided to the applicable care home staff prior to the trial commencing. CRFs should be completed in black ball point pen, with unique service user ID number, Study Medication Number (where applicable) initials and date of birth recorded on the header of each individual form. Incorrectly entered information should only be amended on the original CRF prior to photocopying. Corrections should be made by deleting with a single line through the entry and writing the correct value alongside the box; all amendments should be initialled and dated. CRFs will be Non carbon copied where possible. The top copy should be sent to the PAAD TM or picked up by the SEWTU PAAD team/research nurse and the bottom copy kept in the SU PAAD file.

13.3.1 Allocation of study medication

The procedure for allocation of study medication is detailed in Section 9.6.1

13.3.2 Baseline assessments

Following the completion of the Eligibility for Study Medication CRF, baseline assessments will take place. Using the Medical Information CRF the SUs clinical frailty and nutritional status will be recorded, as well as a detailed list of medical history and concurrent medication. The EQ-5D Quality of Life questionnaire will also be completed at this time point.

13.4 Follow-up

Service Users prescribed with antibiotics will be followed up for eight weeks from the date that they are allocated study medication.

13.4.1 Daily Diary

A diary will be kept for an eight week follow-up period. The diary will record information on adherence to the study intervention over the 21 day period and for the antibiotic

treatment period; study adverse events and symptoms related to diarrhoea severity and illness severity.

13.4.2 Stool Chart

For each week of the study follow-up period, a stool chart will record the frequency and type of stool (according to the BSC).

13.4.3 Quality of Life

Health-related quality of life will be assessed at the beginning of each week for the duration of the eight-week follow-up period via the EQ-5D.

13.4.4 Healthcare Resource Usage

A record of the healthcare resource usage will be collected for each service user at the end of the 8 week follow-up period. This enables an assessment of any use of NHS resources, (including GP and practice nurse consultations, procedures, investigations, hospital appointments, A&E attendances and any hospital inpatient admissions).

13.4.5 Medication use

A record of the medication used post randomisation for the 8 weeks of follow up will be collected.

13.4.6 Stool sampling

Diagnostic stool samples will be collected only at times when diarrhoea occurs during follow up and a second sample will be collected if diarrhoea continues for greater than 48 hours. Diarrhoea, for the purposes of this study, is defined as 3 or more loose stools at BSC type 5 – 7, in a 24 hour period, following a period of normal stool consistency. Sampling will be carried out by a CHS / study research nurse. The sample will be put into containers provided by the study team. This container must be labelled with the participants ID number, initials and date of birth and sent by 1st Class Royal Mail using Post Office approved Safeboxes^{TM}, a method that meets legal requirements. The sample must be sent within 48 hours of taking the sample, in order to be analysed within 72 hours. The sample will be sent to the Public Health Wales Microbiology laboratory for the determination of microbial content, speciation of *C. difficile* culture, toxins A and B and as well as screening for carriage of antibiotic resistant bacteria. Any cultured *C. diff* isolates will be ribo-typed, toxin tested, and have antimicrobial sensitivity testing done, as well as screening for carriage of antibiotic resistant bacteria. All isolates will be retained and stored at -70^{o}C.

The research team will receive results of study diagnostic stool sample analyses from the Microbiology laboratory.

Table 1 – CRF schedule

Data Type	Before study recruitment begins	At time of consent	At time of antibiotic prescribed/ eligibility checked and confirmed	Follow Up Period (weeks) 1	2	3	4	5	6	7	8
1. Care Home	X										
2. Eligibility for enrolment		X									
3. Eligibility for Study Medication			X								
a) Medical information			X								
4. Follow up diary											
a) Study medication and antibiotic adherence				D	D	D	D				
b) Illness severity and symptoms				D	D	D	D	D	D	D	D
c) Stool monitoring				D	D	D	D	D	D	D	D
d) Additional Medication				W1	W1	W1	W1	W1	W1	W1	W1
e) Quality of life				W2	W2	W2	W2	W2	W2	W2	W2
f) Healthcare resource use											E
5. Diagnostic Stool Sample				I< ---------- as required ---------- >I							
6. Withdrawal		I<---------- as required ---------- >I									
7. SAE				I< ---------- as required ---------- >I							

D = Questions are to be completed on a daily basis

W1 = Questions should be completed on weekly basis for that week

W2 = Questions should be completed at the start of the week based on that day

E = Questions are to be completed at the end of the 8 week follow-up

14 Statistical considerations

14.1 Randomisation

Randomisation will be carried out using random permuted blocks. Computer-generated random numbers will be produced to select a block of allocations from the set of all possible permutations of allocations (on a 1:1 ratio) given a particular block-size before the trial begins.

14.2 Primary outcome measures

The primary outcome is the occurrence of at least one episode of AAD during the eight weeks following randomisation. AAD is defined as three or more loose stools (defined as a 5 – 7 on the BSC) in a 24 hour period following a period of normal stool consistency.

14.3 Secondary outcome measures

- The occurrence of *C.difficile*-associated diarrhoea (CDAD). This is defined as having a diagnostic stool sample (following the occurrence of AAD) that is found to contain *Clostridium difficile* toxin A or B.
- Health-related quality of life measured using the EQ-5D.
- The duration, frequency and recurrence of AAD. The duration of AAD is defined as the total number of consecutive 24 hour periods that a SU has AAD (as per our definition in 14.2.).
- The frequency of AAD is the number of episodes of AAD a SU experiences during the eight week follow-up period. AAD episodes are only considered unique if they are separated by a period of at least three days of "normal" stool consistency
- Recovery from the illness that triggered the prescription of antibiotic treatment. A single item will be asked daily and will capture the illness severity of the SU on a particular day
- Adherence to the study intervention and antibiotic treatment. Adherence will be defined as full (all doses on a particular day), partial (at least one dose but not all) and not (no doses on a particular day).
- Healthcare Resource Use. Costs will incorporate information on GP and practice nurse consultations, other medication, procedures, investigations, hospital appointments, A&E attendances and any hospital inpatient admissions and will be measured at the end of the eight-week follow-up period.
- Unplanned (not a routine hospital appointment) hospitalisation, both all-cause and AAD-related.

- Adverse events. These include reported symptoms such as vomiting, abdominal pain, excessive flatulence, bloating, skin rashes.
- All-causes mortality during the eight week follow-up period.

14.4 Sample size

A total of 400 SUs (200 per arm) will need to be randomised in order to achieve 80% power, at the 5% level, to detect a 50% relative reduction in the incidence of antibiotic associated diarrhoea in those given probiotic intervention alongside antibiotic treatment, compared to placebo alongside antibiotic treatment. This sample size has been adjusted for a 20% loss to follow-up/withdrawal.

Taking into consideration the results from the interim analysis performed in PAAD Stage 1 and a more recent interim assessment of antibiotic prescribing and AAD (from first antibiotic prescription), assuming an AAD incidence of 25% in the placebo arm (lower confidence limit quoted in Appendix 3), in order to randomise 400 SUs we will need to obtain advanced consent from at least 607 SUs (assuming 66% will be prescribed at least one course antibiotics during the 12 month monitoring period and subsequently randomised) and will need to approach approximately 1214 SUs in order to achieve this consent rate (assuming only 50% will provide consent). With an average of 60 SUs per home, we will need to recruit from a minimum of 21 care homes. In order to allow for care home drop-out, larger than anticipated withdrawals/drop-out/declines and smaller than anticipated care homes, we aim to recruit from 24 care homes.

15 Analysis

15.1 Main analysis

For the primary analysis, a logistic regression model will be constructed with AAD during eight week follow-up (Yes/No) as the dependent variable and study arm (probiotic/placebo) as an explanatory variable. The analysis will be adjusted for:

- The potential clustering of SUs within care homes via multilevel analysis
- Potential, pre-specified confounding/risk factors as specified in the Statistical Analysis Plan

The primary analysis will be based on the intention to treat principle.

15.1.1 Secondary analyses

In a similar way to the primary analysis, a logistic regression model will be constructed, with 'Returned positive stool sample for *Clostridium difficile* toxin A and B following AAD' (YES/No) as the dependent variable and study arm (probiotic/placebo) as an explanatory variable, in order to investigate the effect of probiotics on the development of CDAD during the eight week follow-up period. In an analogous way to the primary, this analysis will adjust for clustering (if present) and confounding factors.

Generalised linear models will be used to order to:

- Investigate the effect of probiotics on the duration, frequency and recurrence of AAD during the eight week follow-up period
- Investigate the effect of probiotics on all-cause hospitalisations during the eight week follow-up period
- Investigate the effect of probiotics on illness recovery
- Investigate the effect of probiotics on antibiotic adherence
- Investigate the relationship between study intervention adherence and AAD/CDAD
- Investigate the relationship between antibiotic adherence and AAD/CDAD
- Investigate the effect of probiotics on mortality in the eight week follow-up period
- Investigate the effect of probiotics on both all-cause and AAD-related hospitalisation during the eight week follow-up period

15.1.2 Sub-group & interim analysis

There is no planned interim analysis for this study.

15.2 Cost effectiveness analysis

Mean differential costs between the two groups will be estimated. As cost data are often skewed, non-parametric bootstrapping methods will be used to test for differences in costs between groups [27]. (Unless one intervention is dominant (lower cost greater effect), results will be reported in the form of an incremental cost utility ratio (cost/QALY). A cost effectiveness acceptability curve will show the probability of the more costly intervention having an incremental cost utility ratio below a range of acceptability thresholds [28].

15.3 Data storage & retention

All data will be kept for 15 years in line with Cardiff University's Research Governance Framework Regulations for clinical research. This data will be stored confidentially on password protected servers maintained on the Cardiff University Network.

Electronic data will be stored on fire-walled University computers, and only accessible to researchers involved in the study. All procedures for data storage, processing and management will be in compliance with the Data Protection Act 1998. All paper records will be stored in a locked filing cabinet, with keys available only to the trial management team. The Trial Statistician will carry out analysis. All essential documents generated by the study will be kept in the trial master file.

16 Study closure

The end of the study will be considered as the date on which the last participant has completed their follow-up assessment.

For the purpose of regulatory requirements the end of the study is defined as the end of the follow-up period of the last recruited SU. For the purpose of the research ethics committee the study end date is deemed to be the date of last data capture.

17 Regulatory and ethical issues

17.1 CTA

This clinical trial has been registered in the EudraCT database and Clinical Trials Authorisation (CTA) will be obtained from the Medicines and Healthcare products Regulatory Agency (MHRA) prior to the start of the study in accordance with Part 3, Regulation 12 of the UK Statutory Instrument.

17.2 Ethical and governance approval

The trial will be conducted in accordance with the recommendations for physicians involved in research on human participants adopted by the 18th World Medical Assembly, Helsinki 1964 and later revisions.

Research governance approval will be granted by Research and Commercial Development at Cardiff University.

This study protocol has been submitted to a Research Ethics Committee (REC) recognised by the United Kingdom Ethics Committee Authority for review and approval. A favourable ethical opinion has been obtained from the REC prior to the commencement of any trial procedures.

All substantial protocol amendments must be approved by the REC responsible for the study, in addition to approval by NHS R&D (and MHRA approval if applicable to the amendment). Minor amendments will not require prior approval by the REC.

If the study is stopped due to adverse events it will not be recommenced without reference to the REC responsible for the study.

The outcome of the study (e.g. completed) will be reported to the REC responsible for the study within 90 days of completion of the last patient's final study procedures. In the event of the study being prematurely terminated a report will be submitted to the REC responsible for the study within 15 days.

A summary of the Clinical Trial Report will be submitted to the REC responsible for the study within one year of completion of the last subject's final study procedures.

17.3 Ethical Conduct of the Study

The Chief Investigator and the Co-Investigators shall be responsible for ensuring that the clinical study is performed in accordance with the following:

- Declaration of Helsinki (Seoul, 2008; Appendix 1).
- ICH Harmonised Tripartite Guideline for Good Clinical Practice.
- The Medicines for Human Use (Clinical Trials) Regulations 2004 [26] (Statutory Instrument 2004 No. 1031) as amended by the Medicines for Human Use (Clinical Trials) Amended Regulations 2006 (Statutory Instrument 2006 No. 1928 and No. 2984) and Amended Regulations 2008 (Statutory Instrument 2008 No. 941).
- Research Governance Framework for Health and Social Care (Welsh Assembly Government 2nd Edition, September 2009 and Department of Health 2nd Edition, July 2005)

17.4 Risks and benefits for trial participants and society

The proposed study does pose ethical issues, namely the conduct of a randomised placebo controlled trial in a population with the potential challenge of mental capacity. For this reason, prior to enrolment and at randomisation, the mental capacity of all SUs will be assessed by trained CHS. In case of reduced capacity, the personal legal representative or the professional legal representative will be approached for the provision of consent.

Due to randomisation of the population involving a placebo, not all service users will receive an intervention of clinical benefit. The question to be answered by the research is whether the consumption of a probiotic during treatment with an antibiotic, effectively prevents AAD and how this impacts not only the clinical care but also the effect on cost of managing care home residents.

From the NHS perspective, the cost of treating AAD in care homes poses a substantial burden on care provided to residents and the prescription rate of antibiotics within the NHS. However it should be noted that costs to the NHS would be incurred if they require primary care, e.g., GP visits and prescriptions or admissions to hospital.

Under the current proposal by the MHRA on risk based approaches to conduction of CTIMPs, the MHRA consider this study to be an efficacy study of VSL$^{\#}$3 in a new and unlicensed indication and have defined this study to be a Type B trial, which identifies the risk to SUs as being somewhat higher than that of standard medical care.

The study medication will be delivered by appropriately trained and experienced care home- clinical staff or study trained staff, managed and monitored by SEWTU.

17.5 Confidentiality

The Chief Investigator and the research team will preserve the confidentiality of participants in accordance with the Data Protection Act 1998.

. All data will be handled according to the principles of the Data Protection Act, especially for sensitive, personal data. Data will be anonymised and stored on a password protected computer located in secure University buildings and appropriately backed up. Any data transfer will be closely monitored. A privacy risk assessment will proactively identify and ameliorate risks of breaches of confidentiality and clearly designate the named individuals who will be allowed to access identifiable information. All data will be retained for up to 15 years post study closure in line with Cardiff University's procedures.

17.6 Indemnity

Cardiff University will provide indemnity and compensation in the event of a claim by, or on behalf of participants, for negligent harm as a result of the study design and/or in respect of the protocol authors/research team. Cardiff University does not provide compensation for non-negligent harm.

17.7 Study sponsorship

This study is sponsored by Cardiff University, under the governance of the Research and Development Commercial Division. Delegated responsibilities will be assigned to the NHS trusts taking part in this study.

17.8 Funding

This study is funded by the Department of Health via the Health Technology Assessment (HTA) programme.

17.9 Audits & inspections

The study is open to inspection by HTA as the funding organisation. The study may also be participant to inspection and audit by Cardiff University under their remit as sponsor. As this study is classified as a clinical trial of investigational medicinal products (CTIMP), it may also be participant to inspection by the MHRA.

18 Study management

18.1 Internal Project Team

This group will consist of the Chief Investigators and the Trial Management Team within SEWTU and will meet at least fortnightly to discuss the day-to-day issues that arise from the study. All important discussions will be relayed to the TMG for final decision.

18.2 Trial Management Group

The TMG will consist of the Chief Investigator, Co-Applicants, a member of the CHS, a lay representative, TM, Trial Statistician and Trial Administrator. The role of the TMG will be to help set up the study by providing specialist advice, input to and comment on study procedures and documents (information sheets, protocol, etc). They will also advise on the promotion and running of the trial and deal with any issues that arise. The group will meet monthly throughout the course of the study.

18.3 TSC (Trial Steering Committee)

A TSC will be established and will meet at least 6 monthly. It will comprise an independent chair and three other independent members. This committee will provide independent oversight of the study.

The committee will be chaired by Dr Peter Crome, Professor of Geriatric Medicine, Research Institute of Life Course Studies, Keele University, who has extensive clinical trials expertise as well as expertise in the care of the elderly.

The first meeting will be before the study commences to review the protocol and arrange the timelines for the subsequent meetings. The TSC will provide overall supervision for the trial and provide advice through its independent chair. The ultimate decision for the continuation of the trial lies with the TSC, after discussion with the TMG.

18.4 IDMC (Independent Data Monitoring Committee)

In order to monitor accumulating data on safety and any study intervention benefit, an independent data monitoring committee (IDMC) will be established. The IDMC will act as an advisory body to the TSC and will meet annually.

19 Data monitoring and quality assurance

Regular monitoring will be performed according to ICH GCP and the trial monitoring plan. Data will be evaluated for compliance with the protocol and accuracy in relation to source documents. Following written standard operating procedures, the monitors will verify that the study is conducted and data are generated, documented and reported in compliance with the protocol, GCP and the applicable regulatory requirements.

20 Publication policy

All publications and presentations relating to the study will be authorised by the TMG and will be in accordance with the study's publication policy.

21 References

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22 Appendices

Appendix 1 - Declaration of Helsinki

Adopted by the 18th WMA General Assembly, Helsinki, Finland, June 1964, and amended by the:
29th WMA General Assembly, Tokyo, Japan, October 1975
35th WMA General Assembly, Venice, Italy, October 1983
41st WMA General Assembly, Hong Kong, September 1989
48th WMA General Assembly, Somerset West, Republic of South Africa, October 1996
52nd WMA General Assembly, Edinburgh, Scotland, October 2000
53rd WMA General Assembly, Washington 2002 (Note of Clarification on paragraph 29 added)
55th WMA General Assembly, Tokyo 2004 (Note of Clarification on Paragraph 30 added)
59th WMA General Assembly, Seoul, October 2008

A. INTRODUCTION

1. The World Medical Association (WMA) has developed the Declaration of Helsinki as a statement of ethical principles for medical research involving human subjects, including research on identifiable human material and data.
   The Declaration is intended to be read as a whole and each of its constituent paragraphs should not be applied without consideration of all other relevant paragraphs.
2. Although the Declaration is addressed primarily to physicians, the WMA encourages other participants in medical research involving human subjects to adopt these principles.
3. It is the duty of the physician to promote and safeguard the health of patients, including those who are involved in medical research. The physician's knowledge and conscience are dedicated to the fulfilment of this duty.
4. The Declaration of Geneva of the WMA binds the physician with the words, "The health of my patient will be my first consideration," and the International Code of Medical Ethics declares that, "A physician shall act in the patient's best interest when providing medical care."
5. Medical progress is based on research that ultimately must include studies involving human subjects. Populations that are underrepresented in medical research should be provided appropriate access to participation in research.
6. In medical research involving human subjects, the well-being of the individual research subject must take precedence over all other interests.
7. The primary purpose of medical research involving human subjects is to understand the causes, development and effects of diseases and improve preventive, diagnostic and therapeutic interventions (methods, procedures and treatments). Even the best current interventions must be evaluated continually through research for their safety, effectiveness, efficiency, accessibility and quality.
8. In medical practice and in medical research, most interventions involve risks and burdens.
9. Medical research is subject to ethical standards that promote respect for all human subjects and protect their health and rights. Some research populations are particularly vulnerable and need special protection. These include those who cannot give or refuse consent for themselves and those who may be vulnerable to coercion or undue influence.

10. Physicians should consider the ethical, legal and regulatory norms and standards for research involving human subjects in their own countries as well as applicable international norms and standards. No national or international ethical, legal or regulatory requirement should reduce or eliminate any of the protections for research subjects set forth in this Declaration.

B. BASIC PRINCIPLES FOR ALL MEDICAL RESEARCH

11. It is the duty of physicians who participate in medical research to protect the life, health, dignity, integrity, right to self-determination, privacy, and confidentiality of personal information of research subjects.
12. Medical research involving human subjects must conform to generally accepted scientific principles, be based on a thorough knowledge of the scientific literature, other relevant sources of information, and adequate laboratory and, as appropriate, animal experimentation. The welfare of animals used for research must be respected.
13. Appropriate caution must be exercised in the conduct of medical research that may harm the environment.
14. The design and performance of each research study involving human subjects must be clearly described in a research protocol. The protocol should contain a statement of the ethical considerations involved and should indicate how the principles in this Declaration have been addressed. The protocol should include information regarding funding, sponsors, institutional affiliations, other potential conflicts of interest, incentives for subjects and provisions for treating and/or compensating subjects who are harmed as a consequence of participation in the research study. The protocol should describe arrangements for post-study access by study subjects to interventions identified as beneficial in the study or access to other appropriate care or benefits.
15. The research protocol must be submitted for consideration, comment, guidance and approval to a research ethics committee before the study begins. This committee must be independent of the researcher, the sponsor and any other undue influence. It must take into consideration the laws and regulations of the country or countries in which the research is to be performed as well as applicable international norms and standards but these must not be allowed to reduce or eliminate any of the protections for research subjects set forth in this Declaration. The committee must have the right to monitor ongoing studies. The researcher must provide monitoring information to the committee, especially information about any serious adverse events. No change to the protocol may be made without consideration and approval by the committee.
16. Medical research involving human subjects must be conducted only by individuals with the appropriate scientific training and qualifications. Research on patients or healthy volunteers requires the supervision of a competent and appropriately qualified physician or other health care professional. The responsibility for the protection of research subjects must always rest with the physician or other health care professional and never the research subjects, even though they have given consent.
17. Medical research involving a disadvantaged or vulnerable population or community is only justified if the research is responsive to the health needs and priorities of this population or community and if there is a reasonable likelihood that this population or community stands to benefit from the results of the research.
18. Every medical research study involving human subjects must be preceded by careful assessment of predictable risks and burdens to the individuals and communities involved in the research in comparison with foreseeable benefits to them and to other individuals or communities affected by the condition under investigation.
19. Every clinical trial must be registered in a publicly accessible database before recruitment of the first subject.

20. Physicians may not participate in a research study involving human subjects unless they are confident that the risks involved have been adequately assessed and can be satisfactorily managed. Physicians must immediately stop a study when the risks are found to outweigh the potential benefits or when there is conclusive proof of positive and beneficial results.
21. Medical research involving human subjects may only be conducted if the importance of the objective outweighs the inherent risks and burdens to the research subjects.
22. Participation by competent individuals as subjects in medical research must be voluntary. Although it may be appropriate to consult family members or community leaders, no competent individual may be enrolled in a research study unless he or she freely agrees.
23. Every precaution must be taken to protect the privacy of research subjects and the confidentiality of their personal information and to minimize the impact of the study on their physical, mental and social integrity.
24. In medical research involving competent human subjects, each potential subject must be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail, and any other relevant aspects of the study. The potential subject must be informed of the right to refuse to participate in the study or to withdraw consent to participate at any time without reprisal. Special attention should be given to the specific information needs of individual potential subjects as well as to the methods used to deliver the information. After ensuring that the potential subject has understood the information, the physician or another appropriately qualified individual must then seek the potential subject's freely-given informed consent, preferably in writing. If the consent cannot be expressed in writing, the non-written consent must be formally documented and witnessed.
25. For medical research using identifiable human material or data, physicians must normally seek consent for the collection, analysis, storage and/or reuse. There may be situations where consent would be impossible or impractical to obtain for such research or would pose a threat to the validity of the research. In such situations the research may be done only after consideration and approval of a research ethics committee.
26. When seeking informed consent for participation in a research study the physician should be particularly cautious if the potential subject is in a dependent relationship with the physician or may consent under duress. In such situations the informed consent should be sought by an appropriately qualified individual who is completely independent of this relationship.
27. For a potential research subject who is incompetent, the physician must seek informed consent from the legally authorized representative. These individuals must not be included in a research study that has no likelihood of benefit for them unless it is intended to promote the health of the population represented by the potential subject, the research cannot instead be performed with competent persons, and the research entails only minimal risk and minimal burden.
28. When a potential research subject who is deemed incompetent is able to give assent to decisions about participation in research, the physician must seek that assent in addition to the consent of the legally authorized representative. The potential subject's dissent should be respected.
29. Research involving subjects who are physically or mentally incapable of giving consent, for example, unconscious patients, may be done only if the physical or mental condition that prevents giving informed consent is a necessary characteristic of the research population. In such circumstances the physician should seek informed consent from the legally authorized representative. If no such representative is available and if the

research cannot be delayed, the study may proceed without informed consent provided that the specific reasons for involving subjects with a condition that renders them unable to give informed consent have been stated in the research protocol and the study has been approved by a research ethics committee. Consent to remain in the research should be obtained as soon as possible from the subject or a legally authorized representative.

30. Authors, editors and publishers all have ethical obligations with regard to the publication of the results of research. Authors have a duty to make publicly available the results of their research on human subjects and are accountable for the completeness and accuracy of their reports. They should adhere to accepted guidelines for ethical reporting. Negative and inconclusive as well as positive results should be published or otherwise made publicly available. Sources of funding, institutional affiliations and conflicts of interest should be declared in the publication. Reports of research not in accordance with the principles of this Declaration should not be accepted for publication.

C. ADDITIONAL PRINCIPLES FOR MEDICAL RESEARCH COMBINED WITH MEDICAL CARE

31. The physician may combine medical research with medical care only to the extent that the research is justified by its potential preventive, diagnostic or therapeutic value and if the physician has good reason to believe that participation in the research study will not adversely affect the health of the patients who serve as research subjects.
32. The benefits, risks, burdens and effectiveness of a new intervention must be tested against those of the best current proven intervention, except in the following circumstances:
    - The use of placebo, or no treatment, is acceptable in studies where no current proven intervention exists; or
    - Where for compelling and scientifically sound methodological reasons the use of placebo is necessary to determine the efficacy or safety of an intervention and the patients who receive placebo or no treatment will not be subject to any risk of serious or irreversible harm. Extreme care must be taken to avoid abuse of this option.

33. At the conclusion of the study, patients entered into the study are entitled to be informed about the outcome of the study and to share any benefits that result from it, for example, access to interventions identified as beneficial in the study or to other appropriate care or benefits.
34. The physician must fully inform the patient which aspects of the care are related to the research. The refusal of a patient to participate in a study or the patient's decision to withdraw from the study must never interfere with the patient-physician relationship.
35. In the treatment of a patient, where proven interventions do not exist or have been ineffective, the physician, after seeking expert advice, with informed consent from the patient or a legally authorized representative, may use an unproven intervention if in the physician's judgement it offers hope of saving life, re-establishing health or alleviating suffering. Where possible, this intervention should be made the object of research, designed to evaluate its safety and efficacy. In all cases, new information should be recorded and, where appropriate, made publicly available.

APPENDIX 2 : Interim analysis for PAAD Stage 1

Appendix 2 – Summary of analysis relating to stopping rules from stage 1 (observational study) to stage 2 RCT

Outcome	Stop if:	Estimate	Result (proceed/stop)
Recruitment	The proportion of residents recruited is less than 60% of those approached.	260/363 = 72% (95% Confidence Interval: 67% – 77%)	Proceed
Antibiotic prescribing	The proportion of recruited residents prescribed at least one course of antibiotics is less than 27%	119/260 = 46% (95% Confidence Interval: 40% – 52%)	Proceed
Antibiotic Associated Diarrhoea (AAD)	The proportion of antibiotic prescriptions (with follow-up data) resulting in at least one episode of AAD is less than 18%	51/152 = 34% (95% Confidence Interval: 25% –42%)*	Proceed
Severe AAD*	The proportion of antibiotic prescriptions resulting in at least one episode of AAD is less than 18% and the proportion of AAD episodes classed as severe is low	There were no episodes of AAD lasting longer than two weeks. Of the 34 diagnostic stool samples received and analysed, 8 (24%) were found to have *C. difficile*. There we no episodes of AAD that resulted in hospitalisation or death.	Proceed

† Severe AAD is defined as AAD that (any of the following): lasts for more than two weeks, results in hospitalisation or death, is attributed to C.difficile.

* Presented as the raw proportion with confidence interval adjusted for clustering of prescriptions within service users. The most conservative estimate is presented here (removing episodes that correspond to service users who normally have loose stools and either have them 3+ times or day or a frequency that was unknown).

† Severe AAD is defined as AAD that (any of the following): lasts for more than two weeks, results in hospitalisation or death, is attributed to C.difficile.