NETSCC, HTA

6 February 2012

The PAAD Study

Probiotics for **A**ntibiotic **A**ssociated **D**iarrhoea (including *Clostridium difficile*) in care homes: establishing the platform and a randomised controlled trial

Stage 1: Establishing the platform
Version 7.0 17/08/2011

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Please contact the Study Manager for general queries and supply of trial documentation

Study Queries:

Study Queries

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

Serious Adverse Events

SAE reporting

Where the adverse event meets one of the serious categories an SAE form should be completed by the responsible person and faxed to PAAD Trial Manager within 24 hours upon becoming aware of the event. (See sections 9 for more details)

Fax Number: 02920 687 612

Table of Contents

Glossary of abbreviations and definitions

AE	Adverse Event
CF	Consent Form
CI	Chief Investigator
CRF	Case Report Form
CTU	Clinical Trials Unit
CU	Cardiff University
EudraCT	European Clinical Trials Database
ICH	International Conference on Harmonization
GCP	Good Clinical Practice
GP	General Practitioner
GAfREC	Governance Arrangements for NHS Research Ethics Committees
HTA	Health Technology Assessment
IC	Informed consent
IDMC	Independent Data Monitoring Committee
IEC	Independent Ethics Committee
IMP	Investigational Medicinal Product
ISRCTN	International Standard Randomised Controlled Trial Number
LHB	Local Health Board
MREC	Multi-Centre Research Ethics Committee
PI	Principal Investigator
PIAG	Patient Information Advisory Group
PIS	Patient Information Sheet
QL (QoL)	Quality of Life
R&D	Research and Development
RCT	Randomized Controlled Trial
SAE	Serious Adverse Event
SEWTU	South East Wales Trials Unit
SMF	Study Master File
SMG	Study Management Group
SSC	Study Steering Committee
SSI	Site Specific Information
SUSAR	Suspected Unexpected Serious Adverse Reactions

Definitions:

Antibiotic Associated Diarrhoea (AAD) is defined as "three or more loose stools in a 24 hour period during or within 8 weeks of stopping oral or parenteral antibiotic treatment following normal stool consistency on the day commencing the antibiotic" according to the Bristol Stool Form Scale" (adapted KW Heaton, University of Bristol).

C. difficile **Associated Diarrhoea (CDAD)** is defined as "Diarrhoea not attributable to any other cause which occurs at the same time as a positive toxin assay (with or without a positive *C. difficile* culture) or endoscopic evidence of pseudomembranous colitis."

Probiotics

Probiotics are dietary supplements containing a mono- or mixed culture of live micro organisms 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 [1]. Probiotics can be purchased over the counter in pharmacies and supermarkets and are taken by the public on a daily basis

Care Homes

Nursing Home

Residential Home

Dual Registered Care Home

1. Study summary & schema

1.1 Study Summary

PAAD is a two Stage study.

This protocol is for Stage 1 *only*: Establishing the platform.Stage 1: There is currently a lack of evidence regarding; 1) the frequency of antibiotic prescribing and type of antibiotic prescribed in care homes in the UK and, 2) how often diarrhoea occurs associated with taking antibiotics, and its severity.

Nine care homes in South Wales and the care home service users (residents) will be recruited for Stage 1. The main part of Stage 1 is a 12 month prospective ***observational study*** that aims to collect data (e.g. amount and type of antibiotics prescribed episodes of Antibiotic Associated Diarrhoea (AAD) and *Clostridium difficile*-associated diarrhoea (CDAD) and outcome, in a purposive sample of care homes. Additionally, there will be 3 sub-studies within Stage 1.

Main Observational Study

Data regarding indication for prescribing, type of antibiotic, dose, route of administration and duration of antibiotic will be collected each time a participating service user is prescribed antibiotics by their GP. Should a service user who is prescribed antibiotics develop diarrhoea, either during, or within, eight weeks of stopping the antibiotic(s), a stool sample will be collected and sent, as per routine procedure, to the local lab for standard microbiological stool analysis including *C. difficile* analysis as well as to the central lab to test for *C. difficile* and screening for carriage of antibiotic resistant bacteria. A stool chart will be completed for the duration of antibiotic treatment and for an additional eight weeks after the antibiotic course is complete.

Sub-Studies

Sub study 1: C. difficile Prevalence

A baseline stool sample will be collected from care home service users to assess *C. difficile* prevalence in the Care Homes. Data about previous antibiotic use by the service user, for a 3 month period before entry to this sub-study will also be collected.

Sub Study 2 Qualitative Observational Study of Care Home Routines

To account for the known difficulties in conducting research in this setting, we plan to carry out observations of daily care routines within the care homes to gain a greater understanding of how a sample of care homes operate and how this might impact upon a Randomised Controlled Trial to determine the effectiveness of probiotics given alongside antibiotics in reducing Antibiotic Associated Diarrhoea.
In order to achieve this, we plan to observe a range of daily care routines and features of care homes participating in PAAD stage 1, in order to inform the design of PAAD stage 2.

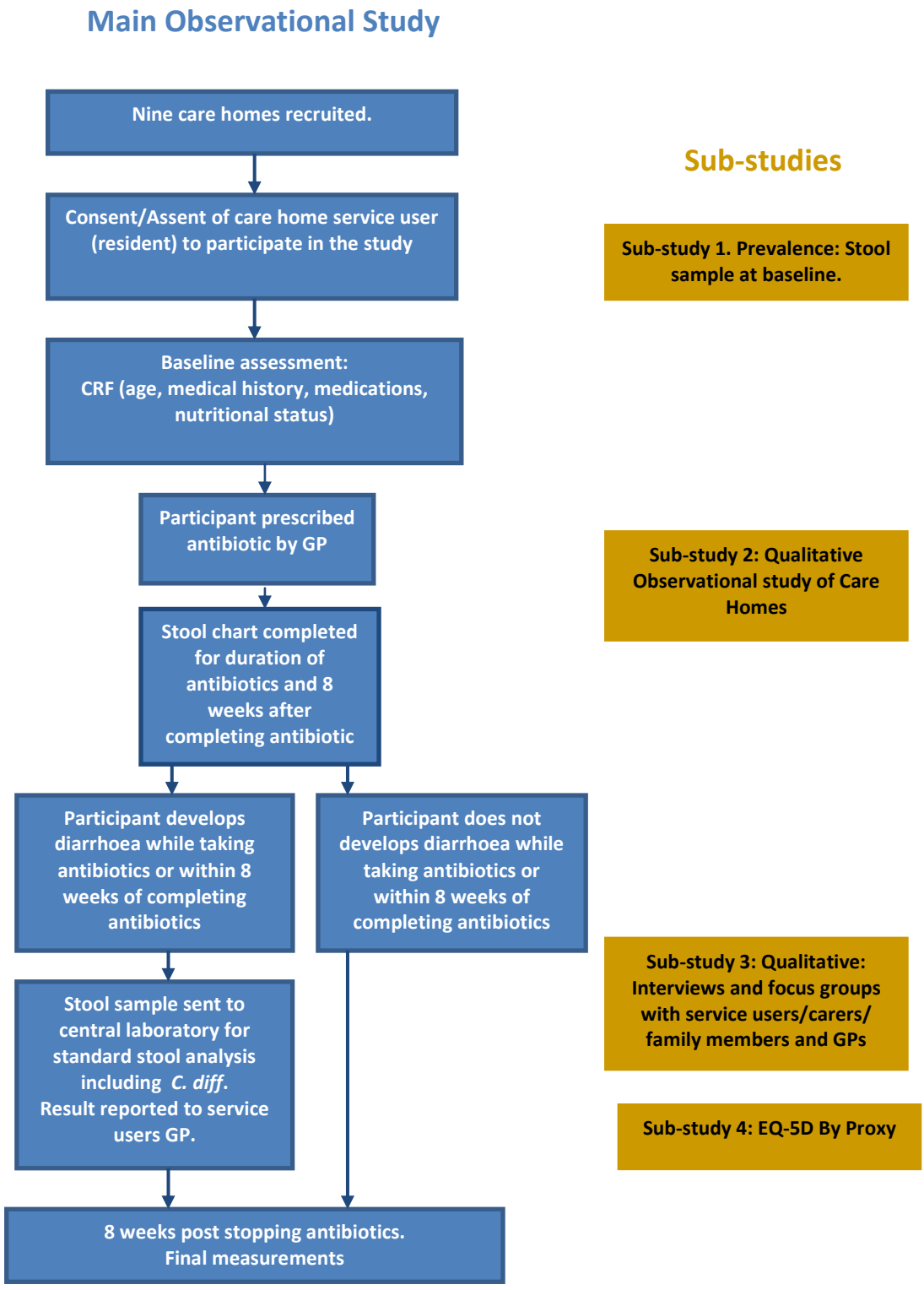
Sub study 3: Qualitative Study
1) Qualitative interviews will be conducted with service users capable of consent, and 2) focus groups will be conducted with family members and care home staff discussing issues around consent and assent in care home residents. 3) Additional interviews with GPs regarding these issues will also be conducted.
The focus groups and interviews will also take into account issues from sub study 2 (above). For more details on Sub-Study 3, see Section 17.3

Sub study 4 - Measuring quality of life by proxy in care homes: An exploration of differences between proxy types (EQ-5D by Proxy)
The EQ-5D questionnaire is a well-established method of assessing Health Related Quality of Life (HRQol (www.euroqol.org) and is preferred by the National Institute for Health and Clinical Excellence for use in cost utility studies (NICE, 2009). However, there are problems associated with obtaining responses to HRQoL questions from those who are restricted in their ability to make judgements. This sub- study is testing the hypothesis that there is an inverse relationship between agreement in subject/proxy EQ-5D scores and subject's level of cognitive competence. If results support this hypothesis, then a minimum level of cognitive competence will be identified for which EQ-5D data should be collected by proxy. The study will also explore whether a combination of professional and friend/relative proxies would be preferable to either proxy alone.

In summary, Stage 1 will identify the scale of the AAD problem in care homes, provide reliable incidence data and confirm the basis of our sample size calculation for the randomised controlled trial (RCT) in Stage 2. Stage 1 will also allow us to pilot the trial procedures and materials required for a RCT in Stage 2. If Stage 1 indicates that AAD is a rare, unimportant problem, then, based on explicit stopping rules, we will not progress to Stage 2.

Stage 2 (For information only): If, during Stage 1, the *a priori* specified incidence threshold is met, Stage 2 will be conducted. Stage 2 is a randomised controlled trial to assess whether AAD is prevented or ameliorated in care home service users receiving antibiotics by the administration of a probiotic along side the antibiotic. Based on limited published literature, we estimate that this aspect of the study, Stage 2, will involve 450 service users in 50 care homes in Wales and the South West. However, Stage 1 is being done partly because the evidence to support this sample size calculation is inadequate. At any point during a one year period, if the residents' doctor considers them to have developed an infection that requires antibiotic treatment, they will be randomly allocated to receive either a course of probiotic or an identical placebo together with their prescribed antibiotic.

1.2 Stage 1 study schema



2 Introduction

2.1 Background

2.1.1 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, 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 39% of hospitalised patients receiving antibiotics [2]. Little is known about the incidence of AAD in primary care or care homes.

2.1.2 *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[3]. It has more recently been highlighted as a potentially serious threat to hospitalised patients and care home residents, causing high levels of morbidity and, in some cases, death [4, 5]. The spores of *C. difficile* can survive for lengthy periods in the environment and gut; therefore, there is a high risk of cross infection, either through direct patient-to-patient contact, via healthcare staff, or via a contaminated environment. Routinely collected voluntary surveillance Health Protection Agency (HPA) 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.

2.1.3 *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 (DH website). CDAD occurs most often as a consequence of disruption of the indigenous protective colonic microflora following broad-spectrum antibiotic treatment. *C. difficile* accounts for 20-30% of AAD [6], although some estimates are more conservative [7]. 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 2 months is the most important risk factor for developing CDAD [8]. other well recognised risk factors include age (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 agonists [9-11].

2.1.4 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, residents 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 residents received at least one antibiotic prescription over a twelve-month period [8]. We conducted a prescribing audit of care homes in one Health Authority and found that 134 (7%) of 1901 residents were on an antibiotic on a single day. A study in care homes in Sweden showed 25% of service users were prescribed an antibiotic during a three month observation period.[12] Considerably fewer antibiotics are prescribed in Sweden compared to the UK.[13] We do not know how many of these service users developed AAD nor how many had *C. difficile*. Providing reasonable estimates of these outcomes for the UK relate to the scientific importance of our study to the NHS. Diarrhoea within long term care facilities can cause fatalities and may become endemic. Up to 33% of patients in secondary care in the UK develop diarrhoea after antibiotic treatment.

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 form 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 [14]. 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 [15, 16]

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) [17].

2.1.5 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 [1]. 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 a treatment for antibiotic-associated diarrhoea, including *C. difficile*, as they reinforce the human intestinal barrier and help maintain the commensal gut flora [2, 18-20]. 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. Probiotics are generally well tolerated and free of adverse effects, although theoretically, the introduction of live bacteria may carry the risk of introducing antimicrobial resistance genes. In additional, there are a small number of case reports where probiotic organisms may themselves have caused infection.

A meta-analysis of 10 randomised, blinded placebo-controlled trials included 1862 pediatric and adult patients who received Lactobacillus as a single agent regimen or placebo to prevent AAD. The combined risk ratio 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 held true for adults but not pediatric patients (RR 0.24, 95% CI 0.08-0.75 and RR 0.44, 95% CI 0.18-1.08, respectively)[21]

2.1.6 Conducting research in care homes

Conducting research studies in care homes, especially in nursing homes, poses unique challenges. Care home research participants are more likely to be older, more physically frail and more likely to be cognitively impaired compared to participants from other research settings [22]. 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 [23]. Junior care home staff turnover is

frequent, though senior staff tends to remain in post long-term. Very little scientifically robust research has been conducted in care homes world wide including 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.

2.2 Rationale for current Study

US and UK 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 residents, but this has never been evaluated in a robust clinical trial. Before a trial is justified, the importance of the AAD problem to both the Independent Care Home sector and NHS, as well as a firm basis for sample size calculation and trial methodology need to be more clearly established (Stage 1).

To account for the anticipated difficulties, and to address unanticipated problems in conducting research in the care home setting, we plan to include sub studies within Stage 1 to inform and pilot procedures for the RCT in Stage 2. The sub-studies will test study procedures including giving the probiotic, model consent procedures, develop training materials for care home staff in how to conduct the RCT and determine if cascading of the training to new colleagues is possible. During Stage 1, the reliability of care home staff in identifying and recording aspects of diarrhoea episodes will also be established.

We will also conduct focus groups and qualitative interviews in order to broaden our understanding of consent in this vulnerable population.

3 Study objectives (Stage 1)

To establish the importance of the problem of AAD to service users, their families, care homes and the NHS, provide a firm basis for sample size calculation and ascertain the practicalities of conducting a randomised controlled trial in the care home setting.

3.1 Primary objectives

Observational study

1) To conduct prospective systematic ascertainment of the incidence of AAD in care homes;

2) To allow an appraisal of the estimated sample size for a Randomised Controlled Trial (RCT) in Stage 2;

3.2 Secondary objectives and sub-study objectives

Observational study

1) To conduct prospective systematic ascertainment of antibiotic use in care homes

2) To estimate the risk of AAD overall and from particular antibiotics in care home settings;

3) To identify barriers and implementation issues in conducting a trial of AAD prevention/amelioration in a care home setting.

Sub Study 1. Prevalence:

1) To determine the prevalence of asymptomatic *C. difficile* carriage in service users within selected care homes.

Sub Study 2 Qualitative Observational Study of Care Home Routines

1) To better understand the range of daily care culture and schedules within care home settings (including delivery of food and drink, communication, skill mix, administration, visiting arrangements, toileting arrangements etc).
2) To determine what level of assistance the care home staff require to deliver the study
3) To assess the level of data we can feasibly collect
4) To assess the best method and timing of drug delivery and administration of probiotic/placebo
5) To determine whether study procedures are likely to be effectively communicated throughout the home.

Sub study 3. Qualitative:

1) To conduct focus groups and individual qualitative interviews with service users, their family, care home staff and General Practitioners. To explore the ethical and practical issues of consent and assent, particularly the topic of advanced consent, for elderly residents who may/may not have capacity to consent

Sub study 4 - EQ-5D By Proxy

1) This sub- study is testing the hypothesis that there is an inverse relationship between agreement in subject/proxy EQ-5D scores and the

subject's level of cognitive competence. If results support this hypothesis, then a minimum level of cognitive competence will be identified below which EQ-5D data should be collected by proxy.

2) The study will also explore whether a combination of professional and friend/relative proxies would be preferable to either proxy alone.

4 Study design

Stage 1 of PAAD is a prospective observational study that will collect initial data (e.g. amount and type of antibiotics used, episodes of AAD and CDAD and outcome) for 12 months on 270 service users in a purposive sample of nine care homes in South Wales. This will identify the scale of the problem, provide incidence data to determine whether the trial (Stage 2) is justified, and if so, provide the basis of our sample size calculation. Certain research procedures for the RCT (Stage 2) will also be piloted and developed within Stage 1.

Within the first Stage there will be three sub studies imbedded within the main study (see section 17 for more details). These are:

1) Prevalence Sub Study:

To establish the asymptomatic carriage of *C. diff* in care home service users in each care home. This will occur during a one-week collection phase in each of the included care homes. This is an optional component for all service users.

Antibiotic prescribing data for the previous three months for each of the service users taking part in this sub study will also be collected. This will provide valuable research information for comparing to the antimicrobial sensitivities of bacterial isolates identified in baseline stool samples.

2) Sub Study 2 Qualitative Observational Study of Care Home Routines

PAAD sub-study 2 is a qualitative observation study which we aim to conduct in 5 of the 10 care homes participating in PAAD stage 1. Care home staff will be informed that a researcher is observing daily care routines. Service users and relatives will not be informed that a researcher is observing daily care routines.

Sub-study 2 is being conducted as a pre-research study (ie. to inform the design of PAAD stage 2) and not a research study.

3) Qualitative Sub Study:

To establish the feasibility and acceptability of taking advance consent/assent for research trial procedures in care home service users. This will be achieved through conduction of 18 focus groups with family members and care staff, and qualitative interviews with GPs and service users at nine homes.

4) EQ-5D by Proxy

This is an observational sub study involving up to 150 service users, their main carer and their most frequent visitor. Two of the larger Care Homes already recruited to the main PAAD study will be included in this sub-study so that the maximum number of SUs can be recruited from a minimum number of care homes. Consented SUs will be asked to complete the EQ-5D+C (a standard EQ-5D with one additional question for self-reported cognitive ability) with explanation from an independent researcher. If the SU is able to provide responses to the EQ-5D+C on this occasion, they will also be asked to complete the Mini-Mental State Examination (MMSE) by the researcher. The carer [and most frequent visitor, if available on-site] will be asked to complete two versions of the EQ-5D proxy questionnaire: (i) how the proxy would rate the SU's health (EQ-5D: 1) and (ii) how the proxy thinks the SU would rate his/her own health (EQ-5D: 2).

5 Recruitment of Care Homes

Care Homes located in South East Wales will be approached to take part in the PAAD Study. The Manager of the care homes will be approached to give permission for the care home to take part in the study and for all resident service users to be approached about the study. Each care home will need to have at least three interested staff to take responsibility for conducting the study in their care home. An agreement detailing roles and responsibilities will be signed by the care home manager and Cardiff University. Discussions will be held regarding resources required and implications regarding an increase in *C. difficile* findings.

Care homes will be split into three strata, based on the type of care home: nursing, residential and dual. After care homes in each stratum are identified, corresponding care home managers will be approached at random until three care home managers in each stratum have given permission for their care home to participate in the study. Nine care homes will be recruited in total.

Before any care home can begin recruitment the PAAD Trial Manager will provide the care home with the essential documents to conduct the study. The senior

care home staff / nursing staff will ensure that the following documents have been received by the PAAD Trial Manager:

- The approval letter from the Centre's R&D Department, following submission of the Site Specific Information (SSI) form (if required);
- A signed Study Agreement (care home lead and sponsor signature);
- Completed contacts list of all site personnel working on the Study (see appendix 2);
- Completed Signature List and Roles and Responsibilities document (see appendix 3);
- Consent forms and Patient Information Sheet (PIS) on centre letter headed paper;

In addition to the study specific documents SEWTU will also provide the care home with:

- *C. difficile* Information leaflet;
- A DH Infection Control guidance document for care homes, regarding management of symptomatic service users identified with *C. difficile.*

Upon receipt of all the above documents, the PAAD Trial manager will send a confirmation letter to the care home lead detailing that the centre is now ready to recruit patients into the study. This letter will be filed in each of the care homes Site File. Along with this confirmation letter, any additional documents required to recruit a patient into the PAAD Study will be included.

6 Participant selection

Patients are eligible for the trial if they meet all of the following inclusion criteria and none of the exclusion criteria. All queries about patient eligibility must be directed to the PAAD Trial Manager in the first instance before recruitment.

6.1 Inclusion criteria

1) Service users who are/have been admitted to the care home for >24 hours;
2) Planned admission to care home of one month or more (excludes short term respite care);
3) Provided written confirmed consent/assent provided.

6.2 Exclusion criteria

There are no exclusion criteria for the PAAD Observational Study.

7 Recruitment

7.1 Number of participants

A total of 270 participants will be required for the main observational study of Stage 1.

Due to the age group of the participants and the multiple co-mordities associated with this age group of participants, it is likely that the total number of participants recruited may be reduced during the specified recruitment period. This is expected due to participants who may pass away or withdrew their consent/assent to remain in the study. Any loss in the target number of recruited participants will be compensated by continuing the recruitment period to three months prior to the end of the study. This may result in maintenance of the total number of participants or greater than this target figure.

7.2 Recruitment and consent of service users into main observational study and the prevalence sub study

We will aim to recruit all eligible service users from each care home at the outset and obtain consent or assent to follow them for one year within the main observational study.

There are likely to be two types of service users who are eligible to join the study; those who are have capacity and are able to consent for themselves and those unable to consent for themselves (lack capacity), whereby consent procedures will differ. Either trained senior care home staff / nursing staff or

trained PAAD study research nurses will be responsible for consenting service users.

The following basic steps will be implemented within care homes with local adaption documented.

1. Senior care home staff / nursing staff will identify those service users who are eligible to join the study.
2. Senior care home staff / nursing staff will identify representatives for each service user (i.e. next of kin, those who visit most regularly etc).
3. Senior care home staff / nursing staff or the PAAD research nurses taking consent will assess mental capacity by periodically checking, during the consent procedure, that the information the service user has been given (either the full information sheet or pictorial information sheet, in large print, or verbal explanation) is fully understood by the service user.
4. Where service users have capacity, the service user will sign and date the consent form, with the trained senior care home staff / nursing staff or research nurse taking consent. If the service user consents and agrees, then the service user's representative will be informed that the service user is taking part in the study, and will be sent information about the study.
5. Where service users lack capacity, the service user's representative (consultee) will be provided with information about the study and will be asked for advice about whether or not the service user would want to join the study. The representative will be asked to provide assent for the service user to join the study.
6. If no next of kin or representative can be contacted we will, as suggested by the 2005 Mental Capacity Act s32(3), nominate an appropriate person, e.g. Age Concern Advocate or GP, to give advice. (http://www.opsi.gov.uk/acts/acts2005/20050009.htm).

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

Service user

1) Summary service user information sheet
2) Pictorial service user information sheet
3) Detailed service user information sheet
4) Service user consent form

Service user's representative

1) Detailed consultee information sheet
2) Consultee consent form

We will repeat this process for any new permanent resident moving into participating care homes up to five months following recruitment start in that care home.
The service user / representative must personally sign and date the latest approved version of the informed consent form before any study specific procedures are performed.

The service user / representative will be allowed as much time as wished, to consider the information, and the opportunity to question the care home staff, study research nurse, their GP or other independent parties to decide whether they will participate in the study. Written Informed Consent/Assent will then be obtained by means of participant dated signature and dated signature of the person who presented and obtained the informed consent/assent. The person who obtained the consent/assent must be suitably qualified and experienced, and have been authorised to do so by the Chief Investigator. A copy of the signed Informed Consent/assent will be given to the participants/consultee. The original signed form will be retained at the study site. All consultees who have not responded will be contacted by phone at least once by the care home staff.

7.3 Notifying the service users' GP

A letter will be sent to the service user's GP to notify them that the service user is taking part in the PAAD Study and that stool samples may be taken. Results from diarrhoeal samples will be sent to the GP and care home from the Microbiology Laboratory in the usual manner.

7.4 Screening logs

An anonymous screening log of all ineligible and eligible but not consented/not approached Service Users will be kept at each centre so that any bias from differential recruitment will be detected. The screening log should be sent to the PAAD Trial Manager when all service users have been approached to join the study and those willing to consent have consented.

8 Study procedures

Before any study related procedures are undertaken, the service user's or service user representative's written informed consent will be obtained. Consent to participate in the main observational study for 12 months and consent for the prevalence sub-study 1 will be taken at initial recruitment of service users.
All data forms should be as complete as possible and every effort should be made to collect the data at the desired time points for the appropriate participant.

Table 1 details the PAAD Case Report Form (CRF), time point for data collection and who has overall responsibility for collecting the data. The original CRF will be sent to the PAAD Trial Manager (see contacts for address details) and a copy kept at the care home. The PAAD Study research nurse or NISCHR research nurses/officers, where required, will also able to collect any of the data listed below.

Table 1 Data collection table

CRF	Time point	Collected by
Eligibility/recruitment CRF	Immediately post consent/assent	Care home staff
Baseline CRF	Immediately post consent/assent	Care home staff /Research Nurse
Prevalence Study Stool CRF	Within one week from consent	Care home staff /Research Nurse
Antibiotic CRF	Day of commencement of antibiotic treatment until duration end date	Care home staff /Research Nurse
Stool Chart CRF	Day of commencement of antibiotic treatment, every day for duration of antibiotic + 8 weeks	Care home staff /Research Nurse
Loose Stool CRF	When participant develops diarrhoea.	Care home staff /Research Nurse
Withdrawal CRF	Following a withdrawal	Care home staff
SAE CRF	Following any adverse event	Care home staff

8.1 Body measurements

At baseline, at the time of being prescribed antibiotics and at the end of the eight week follow up, an assessment of body composition/nutrition status (MUST score) will be taken. Where it is not possible to weigh a service home user the Mid Upper Arm Circumference (MUAC) will be done.

8.2 Medication Record

During the collection of Baseline CRF and Antibiotic CRF, a photocopy of the Medication Record from the CARE Home Plan of each consented Service User will be taken either by a member of the Care Home staff registered onto the PAAD study or by one of the Research Officers from the National Institute of Social Health Care Research CRC South East Wales Research Network, (NISCHR, ROs). The photocopy of the medication record will be anonymised by the NISCHR ROs and faxed to the Trial manager at SEWTU. This procedure will be repeated after the service user is prescribed an antibiotic at any time point during the study period.

8.2.1 End of Study Search of Medication Records

At the end of the recruitment period the antibiotics prescribed for each consented service user, as determined from the PAAD Case Record Forms (CRFs), will be checked against the original Medication Records retained with the Care Home Plan for each service user. This data will be collected by Trial Manager, Trial Data Manager, Research Nurses and NISCHR Research Officers. A separate CRF will be designed to transcribe this data.

This procedure will be carried out to determine whether all antibiotics prescribed for service users, recruited at care homes, has been captured as part of the PAAD Observation study.

8.3 Antibiotic CRF and Stool Chart

As soon as the service user has been prescribed an antibiotic, the antibiotic CRF needs to be completed on day 1 and thereafter until the end of the antibiotic course. Every day stools will be assessed based on the Bristol Stool Chart (see Appendix 1) and type noting on the Stool Chart CRF

8.4 Multiple antibiotic prescription during the follow up period

If the service user is advised to stop the antibiotics and then restart or they are given a new prescription of antibiotics within the follow up period, the antibiotic CRF and eight week stool chart should commence again.

8.5 Microbiology and Stool sample collection (baseline prevalence stool and loose stool)

A standardised protocol on when and how to take a stool sample will be provided.

Baseline prevalence stool sample:

The baseline prevalence stool samples will be collected by a care home staff / study research nurse and should be collected within one week of consent. The sample will be put into containers provided by the study team, which are recommended by the Microbiology laboratory. This container will be labelled with the participants ID number, initials and date of birth and sent by 1st Class Royal Mail using Post Office approved Safeboxes™, a method that meets legal requirements. The sample will be sent to the Public Health Wales Microbiology laboratory for *C. difficile* culture and storage at -70°C. 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. Results on baseline samples are for research purposes only and will not be sent back to care homes or GPs. The research team will receive results of study diagnostic stool sample analyses.

Loose Stool sample:

Diagnostic samples (DS) from service users who develop AAD will be sent, as per routine procedure, to local laboratories for routine analysis to include testing for the presence of *C.difficile* toxins A and B, and results will be sent back to the GP, who will subsequently notify the care home of the result. Another sample will be sent, along with the appropriate stool CRF, to central reference laboratory for *C.difficile* culture as above and as well as screening for carriage of antibiotic resistant bacteria. The results of study diagnostic stool sample analyses will be sent to the SEWTU. Expert guidance and support will be given to the care home staff and the GP on how to manage positive results.

8.6 Withdrawal & loss to follow-up

Participants will be given every encouragement to adhere to protocol procedures and follow-up, in order to reduce biases. However, a participant has the right to withdraw consent for participation in any aspect of the PAAD Study at any time.

The participants care will not be affected at any time by declining to participate or withdrawing from the trial.

The care home will inform the PAAD Trial Manager of either death or movement to another facility within eight weeks of being prescribed an antibiotic (the follow up period) for all service users participating in the PAAD Study. Service users will be asked for consent for their care home, primary and secondary health care records (care home and medical records) to be examined and for relevant data to be extracted.

9 Pharmacovigilance

9.1 Definitions

Adverse Event (AE): Any untoward medical occurrence in a study participant.

Serious Adverse Event (SAE): Any untoward and unexpected medical occurrence or effect that:

- Results in death
- Is life-threatening*
- Requires hospitalisation, or prolongation of existing hospitalisation
- Results in persistent/significant disability or incapacity
- Is a congenital abnormality or birth defect
- Is otherwise considered medically significant by the investigator.

*refers to an event during which the participant was at risk of death at the time of the event; it does not refer to an event which might have caused death had it been more severe in nature

Related AE:

The AE resulted from administration of any of the research procedures such as a clinical infection caused by one of the probiotic organisms. (Causal to the research process or intervention)

Unexpected AE:

The event is unexpected and for Sub-study 2; Probiotic feasibility an unexpected event will be any event that is not listed as a known adverse effect.

9.2 Reporting procedures

Reporting responsibilities of the centre:

Where the adverse event meets one of the serious categories an SAE form should be completed by the care home staff allocated responsibility on the delegation of responsibilities log. The SAE form should be faxed to the PAAD study manager within 24 hours upon becoming aware of the event.

Fax Number: 02920 687 612

Evaluating and Reporting:

The designated PAAD clinical assessors will assess the nature of the SAE in Sub study 2: Probiotic feasibility for seriousness, causality and expectedness. The study manager will assess the nature of the SAE in all other cases and refer to clinician if necessary. Following the initial report, follow up data may be requested by the PAAD study Manger. Where the SAE is both related and unexpected the PAAD Trial Manger will notify the main REC within 15 days of receiving notification of the SAE.

10 Study outcomes

10.1 Measures/assessment instruments

Domain	Measure	Collection Method
Sample size calculation	1. Antibiotic prescribing: what, why, dose, route, frequency, duration 2. Number of AAD & CDAD 3. AAD & CDAD Outcome (MUAC/MUST) 4. *C. difficile* asymptomatic carriage	CRF
Piloting Procedures	1. Recruitment and consent 2. Testing data collections tools 3. Acceptability of giving probiotic, 4. QoL completion	CRF Qualitative interview
Develop training materials	1. Training materials	Feedback sessions
Incidence	1. AAD 2. CDAD	CRF

11 Statistical considerations

11.1 Sampling frame and sample size

We will recruit care homes (residential & nursing) within South East Wales. This will be a purposive sample, in that it will ensure contrasting care homes are recruited to include residential, nursing and dual care. The sampling frame will be based on the following criteria:

1) Predominant type of care – residential/nursing/dual

Care homes will be split into three strata, based on the type of care home: nursing, residential and dual. Three from each care homes from each stratum will be recruited to total nine care homes. Recruiting three randomly selected care homes from each of the different strata will allow some insight into the amount of variability between and within different types of care homes (both in terms of the homes themselves and their residents).

Nine care homes will give a sample of approximately 270 Service users. From previous literature, we estimate 40% of care home users are likely to be prescribed antibiotics over a 12 month period. This will enable us to fit a 95% confidence interval to an AAD rate of 25% of +/- 10%. One family focus group around the issues of consent and assent will be conducted in each care home. Additional interviews will be conducted with study participants capable of consent.

11.2 Timing and criteria to justify Stage 2

We will evaluate three months of data collection regarding antibiotic use in nine care homes, together with two additional months of data for AAD. This analysis will provide us with numbers of asymptomatic carriers of *C.diff,* and provide an estimate of numbers of antibiotic prescriptions and AAD including CDAD. The duration and severity of the AAD will also be known.

This data, along with participant consent and follow-up rates, will be used to justify proceeding to a randomised trial in this setting (i.e. Stage 2).

Feasibility components of Stage 1

The feasibility components of Stage 1 are designed to:

Optimise procedures for setting up care homes sites to be able to undertake a clinical trial of an Investigational Medicinal Product (CTIMP);

Optimise informed consent process in a vulnerable population;
Estimate rate of agreement to participate;
Optimise rate of sampling for follow-up.
To identify the minimum level of cognitive competence below which EQ-5D data should be collected by proxy.

If we find that these feasibility components are not met and we identify insurmountable obstacles (e.g. inability to adhere to regulatory requirements within a care home setting), our conclusion would be that more infrastructure and set up work will be needed before such a study can be conducted in this setting.

12 Analysis

12.1 Main analysis

The primary objectives for the main observational study are:

1. To fit a 95% confidence interval around the estimate annual AAD rate which we currently estimate to be 25% based on available evidence.

The secondary objectives for the main observational study are;

1. To describe the type, dose and treatment regimes of the antibiotics taken by service users. We will tabulate each type of antibiotic against the frequency and severity of AAD;
2. To tabulate summary statistics of the incidence of *C. difficile*, the number of repeat cases of diarrhoea, duration from onset and severity.

12.2 Sub-Study analysis

Sub-Study 1. Prevalence:

1. To determine the prevalence of asymptomatic carriage of *C. difficile*.

Sub-Study 2. Qualitative Observational Study of Care Home Routines :

Data gathered on the observation schedule will be collated, entered onto a spreadsheet for ease of comparison, and discussed between the 3 observers. Any inconsistencies will be debated and, if necessary, resolved by a further visit. A short report on the daily care routines will be prepared for each home and sent to the matron for validation. Feedback from this validation process will be incorporated into a final report on the daily care routines of the PAAD care homes which will then be used to inform the design of PAAD stage 2.

Sub-Study 3. Qualitative sub study

Data will be analysed using Framework Analysis. This approach involves the following steps: familiarisation, creating a thematic framework, indexing, charting, mapping and interpretation. The thematic framework will be developed iteratively, informed by the data and agreed during study team meetings. NVivo 8 software will be used for the indexing stage. A proportion (20%) of transcripts will be double coded by more than one researcher. Disagreements about coding will be resolved, where necessary, in a series of study group meetings.

Sub-Study 4. EQ-5D Sub Study

Given the relatively small sample and the exploratory nature of this sub-study, the results will be used to generate hypotheses rather than test them.

Agreement in overall EQ-5D scores between proxies and the SU will be assessed using the Bland/Altman method to estimate 95% limits of agreement.
As data on the individual EQ-5D dimensions are trichotomous (score = 1, 2 or 3) we will use a Kappa statistic to examine agreement between scores obtained from a relative and carer for both SU/proxy on each dimension.
We will also use a Kappa statistic to examine agreement between the carer, research nurse and SU's assessment of the SUs cognitive ability on the day and, via ANOVA, will explore differences between the average MMSE scores and those who said 'yes' or 'no' regarding the SU's level of cognitive ability.
While disagreement between responses by any subject and his/her proxies can clearly be due to factors other than cognitive impairment, it is still anticipated that on average, the level of agreement in each of the above analyses will get closer to the level of agreement for a 'clearly cognitively competent' sub-group alone. These results will allow exploration of the MMSE score below which EQ-5D data should be collected by proxy in the RCT.

13 Study closure

Trial centres will be notified not to collect any further data post the participant closest to the 12 month data collection period month. The study end date is deemed to be the date of last data capture.

14 Regulatory issues

14.1 Ethical approval

Ethics Committee (EC) approval and SSI approval (where required) will be sought through the Integrated Research Application System (IRAS) process. Any substantial changes to the Trial will be sent to the EC for approval and non-substantial sent as notification only. All SAEs that are unexpected and related will be sent to the EC within the appropriate time lines.

The main observational study of Stage 1 raises the following ethical considerations and arrangements:
1) Participants will have provided written informed consent/assent at the outset of the study, before they are prescribed an antibiotic. With their consent, all service users will have a representative identified, to either be approached to provide consent on their behalf or to be notified that the service user is taking part in the study. Consent will be checked at the time of a decision by the GP to prescribe antibiotics for the service user.

2) A central infection control advice centre for all Trial care homes will be selected to deal with the issue of the potential increase in identified *C. difficile* infection.
3) All care home staff will be trained in reporting SAEs and upon receiving an SAE the Chief Investigator (or nominated delegate) will asses the SAE for seriousness, causality and expectedness to determine whether expedited reporting needs to happen.
4) Participants will have the right to withdraw from the trial at any time, without their care being affected.

Sub-Study Considerations:
The prevalence sub-study of *C. difficile* asymptomatic carriage is an optional element to the main observational study. Service users will be able to participate in the observational study of Stage 1 even if they do not wish to enter this sub-study.

For the Qualitative Observational Study of Care Home Routines**,** Care home staff will be informed that a researcher is observing daily care routines. Service users and relatives will not be informed that a researcher is observing daily care routines. This is being conducted as a pre-research study (ie. to inform the design of PAAD stage 2) and not a research study. Therefore consent from care home staff or the service users and their relatives will not be sought.

Consent for the qualitative study will be sought from participants capable of giving consent. It is expected that this sub-study will commence at approximately 5 months after the recruitment start for the main observational study.

For the EQ-5D by Proxy study, the Care Home manager will be approached to give permission for the Care Home to take part in this sub study and for all Care Home Carers and residents to be approached about the sub study. The existing PAAD agreement will be amended to reflect their participation in the EQ5D Sub Study.
All assigned carers in each recruited home will be approached by the researcher, issued with an information sheet about the study, and asked to consent to take part. They will then be asked to identify all service users (SUs) they are assigned to. For each SU, the carer will be asked how long they have been their assigned carer, and if they consider each of their SUs to have general difficulties in their cognitive ability (i.e. competent or non-competent). The carer may ask the researcher any questions they wish about the study.

Each SU will be approached by the researcher, provided with an information sheet about the study, and asked to provide their consent to participate. Again, the SUs can ask any questions they have about the study and may discuss this with their carer, family and friends if they wish. If they do not wish to participate in the study, this will not affect the care they receive in any way. If they would like to participate but are unable to complete questionnaires due to physical difficulties, the researcher can help them by reading the questions and by noting their own responses if required. If they are unable to provide the researcher with consent due to cognitive difficulties, assent will be sought from their assigned consultee.

In this case, the consultee will be provided with an information sheet and asked to provide assent for their SUs participation in the study. If they are agreeable, the SU will be entered into the study.

In the event that SU cannot provide informed consent, when available, the most frequently visiting relative or friend of the consented/assented SU (known as **relative**) will be approached by the researcher, provided with an information sheet, and asked to provide their consent to participate in the study. If they wish to participate, it will then be possible to gather triad data for this SU (i.e. from SU, carer and relative). If the relative does not wish to participate, it will only be possible to gather diad data for this SU (i.e. from SU and carer).

The relative will also be asked to provide details on the nature of their relationship to the SU (e.g. sister, brother, daughter, son, grandchild, friend, etc) and the frequency of their visits (e.g. number of days weekly/monthly/annually.

Participants will have the right to withdraw from the any part of Sub-studies at any time, without their care being affected.

14.2 Data Handling

Electronic data will be stored on fire walled University computers. Files will be password protected and only accessible to researchers responsible for the running of the study and the Chief Investigator. All procedures for data storage, processing and management will be in compliance will the Data Protection Act 1998. All paper records will be stored in a locked filing cabinet, with keys available only to researchers and the chief investigator. The Trial Statistician will carry out analysis. All essential documents generated by the trial will be kept in the Trial Master File.

14.3 Confidentiality

The care home study staff will ensure that the service users' anonymity is maintained. The service user will be identified only by initials, date of birth and a service user ID number on the CRF and any electronic database. All documents will be stored securely and only accessible by trial staff and authorised personnel. The study will comply with the Data Protection Act which requires data to be anonymised as soon as it is practical to do so.

14.4 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.

14.5 Trial sponsorship

Cardiff University will act as sponsor for trial. Delegated responsibilities will be assigned to the Care Homes taking part in this study.

14.6 Funding

This Study is funded by the NIHR HTA.

15 Data monitoring & quality assurance

Direct access will be granted to authorised representatives from the sponsor, host institution and the regulatory authorities to permit trial-related monitoring, audits and inspections.

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

15.1 TSC (Trial Steering Committee)

The TSC will consist of an independent chair, two/three other independent members. The appropriate disciplines will be covered within the TSC members. The Chief Investigator, trial manager and statistician will attend as observers. 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.

15.2 IDMC (Independent Data Monitoring Committee)

The IDMC will consist of an independent chair and two/three other independent members. We will ensure that all appropriate disciplines are covered in choosing the IDMC members. The first meeting will be before the main RCT commences to review the protocol and agree on timelines for interim analyses to take place. The main role of the IDMC is to review the data periodically and make recommendations to the TSC.

15.3 TMG (Trial Management Group)

The TMG will consist of the Chief Investigator, co-applicants and collaborators, Trial Manager, Trial Statistician and Trial Secretary. The role of the TMG is to help set up the study by providing specialist advice, input in and comment on the study procedures and documents (PIS, protocol etc) and advise on the promotion and the running of the trial. The group will meet monthly during the study. This group will also review and advise on the reporting of SAEs.

16 Publication policy

All publications and presentations relating to the study will be authorised by the Trial Management Group. The first publication of the trial results will be in the name of the Trial Management Group, if this does not conflict with the journal's policy. If there are named authors, these will include at least the trial's Chief Investigator, Statistician and Trial Coordinator. Members of the TMG and the Data Monitoring Committee will be listed and contributors will be cited by name if published in a journal where this does not conflict with the journal's policy. Authorship of parallel studies initiated outside of the Trial Management Group will be according to the individuals involved in the project but must acknowledge the contribution of the Trial Management Group and the Study Coordination Centre.

17 PAAD Sub Studies

17.1 Prevalence sub-study

Prevalence of asymptomatic carriage of C. diff and justification

A stool sample will be taken from all consenting service users during a one week collection phase in each of the nine care homes. Antibiotic use data for the previous three months will also be collected from the service users care notes. Service users will be welcome to participate in the remainder of the observational study if they decline to participate in this prevalence sub-study. This prevalence sub-study of asymptomatic carriage of *C. diff* will help establish the magnitude of the problem. CDAD usually occurs in the face of asymptomatic infection, cross

contamination and antibiotic use. Knowing the prevalence of asymptomatic infection and the variation between care homes will therefore inform an appraisal of the seriousness and potential seriousness of the problem, including considering cycling asymptomatic and symptomatic infection between care homes and hospitals. Stool samples will be taken by concentrating a resource in each care home for a single week, as close to the beginning of the study as possible, so that they are supported in recruitment and sampling by a study researcher.

C. diff carriage rates are important to us for the following reasons:

1. We know neither the carriage rate in UK nursing/care homes, nor the variability in carriage between homes, and between different sizes and types of homes. Existing data is old, often derived in outbreak conditions, and obtained in the US and therefore not applicable to the UK, where antibiotic prescribing, organisation of care, and prevalent strains of *C. diff* (e.g. 027) are all different.

2. The risk of a service user developing *C. diff*-associated diarrhoea is greatly affected by the prevalence of *C. diff* colonisation in the home. Service users could be:

a. Colonised with *C. diff*
b. Not colonised with *C. diff,*, but in a home with a high prevalence of *C. difficile* colonisation and therefore with a high likelihood of coming into contact with *C. diff* during antibiotic therapy.

c. Not colonised with *C. diff*, and in a home with no one colonised with *C. diff* and, therefore, at very low risk of contacting it during antibiotic therapy.

If probiotics mainly protect against CDAD rather than other forms of AAD, there is a danger of a type II error if we recruit from homes where service users are mainly in group (c). If probiotics protected against AAD other than CDAD, we would wish to include all care homes in Stage 2. A potentially useful finding could be that probiotics are a useful intervention in homes with a high rate of *C. diff* colonisation (which might be easily predicted by size/nursing dependence etc., data that we will collect in Stage 1 and subject to exploratory analyses of this type).

When the baseline stool sample is collected we will also examine the service users care notes for information about any antibiotics prescribed in the last three

months. This will provide valuable information for comparing to the antimicrobial sensitivities of bacterial isolates identified in baseline stool samples.

17.2 Qualitative Observational Study of Care Home Routines

During the Stage 1, after the initial 6 months of data collection as part of the main observational study, we initiated discussions with the manufacturer of VSL#3 with Care homes as to the procedure of dispensing the study drug or placebo to service users.

From discussions with care homes about the dispensing of the dissolved probiotic in total volume of 100ml water, it was evident that in their experience, service users cannot take such large volumes of liquids as a drink at any one time**.**

Information from the manufacturer of VSL 3 came to light that the study drug can be dissolved in smaller volume if liquids, e.g. 25ml. Furthermore the freeze- dried probiotic can be diluted with cold juices and flavoured water or sprinkled on cold food.

For this reason it has been proposed that Sub-study 2, as previously planned, should be replaced by a qualitative observation study, which will provide detailed analysis of the daily care routines that occur during an 8 hour period in a care home and how these routines will impact the Stage 2 randomised controlled trial, (RCT). The information from this qualitative observation study will provide information on the dispensing and preparation of the probiotic to service users at care homes, in the protocol for the Stage 2 RCT.

17.2.1. Rationale for Qualitative Sub-Study 2

Conducting studies in care homes, especially in nursing homes, poses unique challenges. Recruitment, consent, retention and data collection can be time consuming and difficult and extra time and help should be provided to ensure that the staff in care homes have the potential to carry out the research procedures. Care home staff are also more likely to move after short periods of employment. To account for the known difficulties in conducting research in this setting, we plan to carry out observations of daily care routines within the care homes to gain a greater understanding of how each home operates and how this might impact upon a RCT to determine the effectiveness of probiotics given alongside antibiotics in reducing Antibiotic Associated Diarrhoea.

17.2.2 Overall Objective

To observe a range of daily care routines and features of care homes participating in PAAD stage 1, in order to inform the design of PAAD stage 2.

17.2.3 – Aims

- To better understand the range of daily care culture and schedules within care home settings (including delivery of food and drink, communication, skill mix, administration, visiting arrangements, toileting arrangements etc).
- To determine what level of assistance the care home staff require to deliver the study
- To assess the level of data we can feasibly collect
- To assess the best method and timing of drug delivery and administration of probiotic/placebo
- To determine whether study procedures are likely to be effectively communicated throughout the home.

17.2.4 Study Design

PAAD sub-study 2 is a qualitative observation study. We aim to conduct it in 5 of the 10 care homes participating in PAAD stage 1.
Care home staff will be informed that a researcher is observing daily care routines. Service users and relatives will not be informed that a researcher is observing daily care routines.

Sub-study 2 is being conducted as a pre-research study (ie. to inform the design of PAAD stage 2) and not a research study.

17.2.5 Recruitment and Approach

Observations will be conducted within 5 care homes by one of 3 researchers (DD, HP, FW). Between them these researchers have skills of qualitative research, nursing and dietetics. All three researchers have previous employment experience in care homes. An observation schedule will be used to record topics of interest (see appendix 1). Approximately 6-8 hours of observations will be made in each of the care homes. This time will be conducted in periods of 2 hours. Each care home will be observed by all 3 observers at different times in separate 2 hour sessions. The first care home is a fairly large care home with 3 separate units which operate under different routines. Observation times for this care home will therefore be split.

Home	1a	1b	1c	2	3	4	5
7-9am	FW		HP		DD		FW
9-11am		HP		DD		FW	
11-1pm	HP		DD		FW		HP
1-3pm		DD		FW		HP	
3-5pm	DD		FW		HP		DD
5-7pm		FW		HP		DD	
7-9pm	FW		HP		DD		HP

25 x 2 hour observation sessions in total

Each home between 6-8 hrs observation

Each observer 8-9 x 2 hrs each

17.2.6 Data analysis and reporting

Data gathered on the observation schedule will be collated, entered onto a spreadsheet for ease of comparison, (Appendix 5 – Observational CRF), and discussed between the 3 observers. Any inconsistencies will be debated and, if necessary, resolved by a further visit. A short report on the daily care routines will be prepared for each home and sent to the matron for validation. Feedback from this validation process will be incorporated into a final report on the daily care routines of the PAAD care homes which will then be used to inform the design of PAAD stage 2.

17.2.7 Data analysis and reporting

Data gathered on the observation schedule will be collated, entered onto a spreadsheet for ease of comparison, and discussed between the 3 observers. Any inconsistencies will be debated and, if necessary, resolved by a further visit. A short report on the daily care routines will be prepared for each home and sent to the matron for validation. Feedback from this validation process will be incorporated into a final report on the daily care routines of the PAAD care homes which will then be used to inform the design of PAAD stage 2.

Modifications would be made in time for the start of Stage 2 in the light of this experience. A training package for care home staff will be developed and finalised for use in the main RCT of Stage 2.

17.3 Qualitative Sub study

17.3.1. Rationale for Qualitative Sub-Study 3

There are two stages in PAAD; the first stage is an observational study which does not change current practice nor involve administering any medication. The second stage is a randomised controlled trial of a probiotic versus a placebo (a Clinical Trial of a Medicinal Product (CTIMP)). These two studies are governed by separate laws and regulations in relation to mental capacity. For research outside of Scotland not covered by the Medicines for Human Use (Clinical Trials) Regulations, The Mental Capacity Act (2005)[26] sets out regulations relating to medical research involving adults who lack capacity to consent and the person consulted gives agreement rather than consent. In relation to all clinical trials throughout the UK (and all types of medical research in Scotland), consent to the participation of an adult lacking capacity is given by the legal representative of the participant. The requirements are set out in Schedule 1 to the Medicines for Human Use (Clinical Trials) Regulations 2004.[27] The Clinical Trials (CT) Regulations specify that this consent by a legal representative represents the presumed will of the participant. Thus, PAAD stage 1 is covered by the Mental Capacity Act and personal consultees are able to give agreement to the service user's participation, and PAAD stage 2 is covered by the Medicines for Human Use (Clinical Trials) Regulations and consent is given by a legal representative of the participant.

The PAAD study presents two main challenges relating to consent. First, there are two types of service users who are eligible to join the PAAD study; those who have capacity and are able to consent for themselves, and those who are unable to consent for themselves (lack capacity under the Metal Capacity Act 2005). Trained senior care home staff/nursing staff or trained PAAD study research nurses will be responsible for assessing mental capacity by periodically checking that the information the service user is being given is understood by the service user. In addition the PAAD study (stage 2) presents novel challenges in relation to advanced consent for individuals who both have capacity and lack capacity. Indeed it is feasible that some service users may enter the PAAD study having capacity to consent, and subsequently lose capacity (either temporarily or permanently) due to an illness or deterioration in the health during the 12 months that the PAAD study (stage 2) runs.

For stage one, where service users lack capacity, the service user's representative (personal consultee) will be provided with information about the study and will be asked for advice about whether or not the service user would

want to join the study. The representative will be asked to provide assent for the service user to join the study. If no next of kin or representative can be contacted, an appropriate person will be nominated (nominated consultee) as required by the 2005 Mental Capacity Act s32(3). This person could be a solicitor, an advocate or the service user's GP.

For stage two (a clinical trial of a medicinal product [CTIMP]), where service users lack capacity, a legal representative is required to give consent to the service user participating in the trial. For the majority of service users who lack capacity the written consent of the service user's legal representative, given in co-operation with the treating doctor, is necessary before participation in any clinical trial. A legal representative must not be connected with the conduct of the trial and can be the doctor primarily responsible for the adult's medical treatment, or a professional legal representative.

In addition to the ethical challenges in relation to consent, the PAAD study also potentially raises ethical issues in relation to raising concerns amongst service users, relatives and staff about *C. difficile* within the care home population.

17.3.2. Overall Objective

PAAD sub-study 3 is concerned with exploring some of these ethical and practical challenges using qualitative methods. Our purpose is to optimise the informed consent process in a vulnerable population in preparation for stage two of PAAD.

17.3.3. Aims:

- To collect data on the various merits and problems associated with a number of models of consent for both stage one and stage two of PAAD for service users who either have capacity or lack capacity.
- To establish the view of consultees, service users, staff and GPs regarding participation in two very different studies (observational versus CTIMP)
- To establish the feasibility and acceptability of taking advance consent/assent for research trial procedures (as would be required in stage two) in care home service users.
- To establish views on how the consultees, service users and staff found taking part in the PAAD observational Study (stage one).
- To establish staff views about the study training for staff, the requirements of the study and its impact on the care home including the implications of potentially finding *C. difficile* in the care home population.

- To explore whether service users, staff, relatives, and GPs consider there may be any merit to conducting a trial to examine whether probiotics are able to improve the general health of service users.

17.3.4. Study design

We propose a range of methods to explore these issues with staff, family members, service users (who have capacity to consent to sub-study 3), and GPs who may be asked to act as a consultee for service users in stage 1 and who will be asked to assess eligibly and potentially consent for the service user in Stage 2.

In total we propose to conduct:

- 4 focus groups with care home staff (combined care homes),
- Focus groups or individual interviews with family members
- 9 – 15 face to face semi-structured interviews with GPs (at least one GP from the practice that looks after the care home)
- Approximately 20 face to face semi-structured interviews with service users who have capacity to consent.

17.3.5. Recruitment and approach

(1) Focus groups with care home staff

Care homes have already been asked to nominate 3 key members of staff who will be working on PAAD. These three members of staff from each of the care homes will be invited to participate in a focus group. Information sheets about sub-study 3 will be given to these members of staff. The care home manager will then tell the researchers how many staff from their home will be participating. The focus group will be held at the most convenient time to the homes (during staff lunch breaks or when the required staff are off-duty) and will last no more than an hour and a half to ensure staff are able to resume their duties without too much disruption to the care home. A buffet lunch/tea will be provided for participants and staff will be offered £25 for their time as they will be participating off-duty. The focus group will be held in an appropriate room during the PAAD workshop. Consent forms will be completed at the start of the focus group. Travel expenses will be reimbursed.

Suggested groupings:
Focus group 1. Care Home managers
Focus group 2. Care Home staff

(2) Focus groups with family members

Care homes (or NISCHR Staff) will discuss over the phone, face to face and/or distribute a letter of invitation and an information sheet to the next of kin or close relative. If the relative would like to participate in the focus group they will be asked to inform the care home. The care home (or NISHCR Staff) will then inform the researchers which family members are interested in participating. A suitable date will be chosen that is convenient for the care home which is hosting the focus group. The focus group will be held at lunch time or early evening (to be advised by the care home) and a buffet lunch/light refreshments will be provided. Alternatively the home may chose to run the focus group during one of its regular relative meetings. As with the staff focus group, the relatives' focus group will be grouped according to type of home and geographical area. Travel expenses will be reimbursed.

In the event that care homes do not have regular group meetings with relatives or where group meetings do take place or insufficient numbers of relatives attend these meetings, one to one interviews will be arranged.

Information packs, containing stamped addressed reply cards, wil be distributed to the care homes, who will then approach the relatives/families and hand out the information packs to them to peruse. If interested, the relatives/families can either complete the reply cards and return to the PAAD study team for action or contact the care home, who will inform the PAAD study team for follow-up. Interviews will be conducted within the care homes. In the event that a relative is interested to take part in this sub-study but cannot travel to the care home, the PAAD study staff will conduct the one to one interview at a location agreed with the relative.

Suggested groupings:
Focus group 1. Residential and dual registered homes in Newport
Focus group 2. Nursing homes in Newport
Focus group 3. EMI and dual registered homes in Cardiff/Vale

(3) Interviews with service users
As respondents will need to demonstrate capacity to consent, we anticipate that interviews with service users will only be conducted in residential homes and some dual registered homes. Senior staff will be asked to identify individuals who have capacity to comprehend the nature of PAAD stub study 3. The service users will be asked by care home staff whether they would wish to participate in a short face to face interview. Service users do not have to have given consent to be in

the PAAD study to be approached for sub-study 3 as we may wish to explore their reasons for not participating in the PAAD study. An information sheet will be provided. If the service user agrees, then the researchers will be informed. Interviews will be conducted in a private room at the care home by a research nurse. A consent form will be signed by the service user (or if unable to write, their consent will be witnessed by 2 members of staff).

(4) Face-to-face interviews with GPs.
Care home staff from each of the care homes will be asked to name the main GP (or more than one GP if appropriate) who attends patients within the care home. These GPs will be approached by letter of invitation or phone call to participate in a short face-to-face interview. An information sheet and consent form will also be sent by post. The GPs will then be followed up by a telephone request for an interview. If the GP is willing to be interviewed, the researcher will arrange a suitable time to conduct the interview. A consent form will be signed prior to the interview commencing. We propose to pay the GPs £50 for each interview.

17.3.6. Data collection

We will ask respondents their views of the consent processes that have been used for PAAD stage one and their experiences of participation in PAAD stage one.

We will collect data on the various merits and problems associated with a number of models of consent that will be used for PAAD stage 2 for service users who both have capacity and lack capacity e.g. written consent taken at the beginning of the study and lasting 12 months (regardless of potential loss of capacity during this time); renegotiating written consent at key stages of the trial; written consent at the start of the study and then verbal consent given by service user or their representative (by telephone) every month/key stages thereafter. Discussion will also cover how consent should be taken (e.g. with a witness, over the phone, in person, by post). Respondents will be asked what time frame they feel that advanced consent should cover. The researcher will present the respondent with a range of hypothetical scenarios about taking advanced consent and they will be asked to reflect on the potential advantages and disadvantages. Service users will be asked their opinion on how consent should be taken should they become ill and lose capacity to consent for themselves.

We would also like to collect data on whether service users, staff, relatives and GPs consider it might be worth conducting a trial to examine whether probiotics are able to improve the general health of service users.

The staff focus group discussions will also cover staff views about the study, staff training of study requirements, impact of the study on the care home including the implications of researching *C. difficile* in the care home population.

Data from all focus groups and interviews will be audio-recorded.

The focus groups will be facilitated by FW or HP. Either AA or JN may also be present to co-facilitate and help with audio-recording and refreshments. Face-to-face interviews with service users and GPs will be conducted by FW and HP.

17.3.7. Data analysis

Data will be analysed using thematic analysis using an abductive approach (incorporating themes that have been identified in advance and derived from the data).[28] This approach involves the indexing data according to a thematic framework which is developed iteratively. Qualitative data analysis software (Nvivo v.8) will be used to assist the research team with managing the analysis.[29] FW, HP, AA, JN and AMN will meet to discuss evidence for themes will agree the final framework. Developments in the analytical process will be recorded through a data analysis memo held in Nvivo. A proportion (20%) of the transcripts will be double coded for reliability of coding.

17.3.8. Ethical issues

Ethical approval for PAAD sub-study 3 will be sought as a substantial amendment from the Local Research Ethics Committee.

All potential respondents will be provided with an information sheet. A consent form will be completed prior to data collection. Only service users who have capacity to consent to sub-study 3 will be included in sub-study 3.

17.4 EQ-5D By Proxy Sub study

17.4.1 Background and rationale

The EQ-5D questionnaire is a well-established method of assessing Health Related Quality of Life (HRQoL (www.euroqol.org) and is the preferred instrument for use in cost utility studies by the National Institute for Health and Clinical Excellence (NICE, 2009). However, there are problems associated with obtaining responses

to HRQoL questions from those who are restricted in their ability to make judgements, for example, people with cognitive impairments or dementia (Wolfs et al, 2007, Bryan et al, 2005, Councill et al, 2001).

In these cases, proxies can be employed to respond on behalf of the subject and the Proxy Version of the EQ-5D questionnaire has been tested and shown to be a valid and reliable substitute (www.euroqol.org), but there remain important issues regarding that level of cognitive impairment below which patient reported EQ-5D data may no longer be reliable and use of a proxy is required. Moreover, even where use of data by proxy is indicated, there remain a number of issues regarding which type of proxy would better reflect the subjects' assessment of their own health.

One study found that agreement and reliability of proxy responses tended to be better for relatives, lower for friends and lowest for health care professionals (Andresen et al, 2001). Other evidence further suggests that health professionals may be more reliable in their proxy responses to the more observable dimensions of the EQ-5D instrument (e.g. 'mobility', 'self care') and family members or friends more reliable in the less observable dimensions (e.g. 'anxiety/depression') (Bryan et al, 2005). Anecdotal evidence suggests that, in a residential care setting, all-day carers may have a much better understanding of a person's health-related quality of life than a visiting relative or friend.

Stage 2 of the PAAD Study (the randomised controlled trial) will employ EQ-5D as the measure of HRQoL in the economic evaluation undertaken alongside the trial, and the majority of subjects are expected to exhibit some degree of cognitive impairment. It is, therefore, important to employ the most reliable proxy for reporting the health-related quality of life of residents in care home settings.

17.4.1.1 Terminology

This study involves three different roles that are relevant to gathering quality of life assessments for those with cognitive deficits. For consistency, residents of the care home will be termed as **service user (SU)**, their assigned carer/named nurse will be termed as **carer**, and their relative or friend who visits most frequently will be known as **frequent visitor**.

17.4.2 Sub Study Objectives

This exploratory sub-study is concerned with the hypothesis that there is an inverse relationship between agreement between SU and proxy EQ-5D scores and the SU's level of cognitive competence. If results support this hypothesis, then a minimum level of cognitive competence will be identified below which EQ-5D data should be administered by proxy. The study will also explore whether a

combination of professional and frequent visitor proxies would be preferable to either proxy alone.

17.4.3 Design

This is an observational sub study involving approximately 150 service users, their main carer and their most frequent visitor. (Please see *Figure 1* for a diagram of the study protocol).

17.4.3.1 Recruitment of Care Homes

Two of the larger Care Homes already recruited to the main PAAD study will be included in this sub-study so that the maximum number of SUs can be recruited from a minimum number of care homes. The Care Home Manager will be approached to give permission for the Care Home to take part in this sub study and for all Care Home Carers and residents to be approached about the sub study. The existing PAAD agreement will be amended to reflect their participation in the sub study.

17.4.3.2 Recruitment of Participants

- Carers

All carers in each recruited home will be approached by the researcher, issued with an information sheet about the study, and asked to consent to take part. They will then be asked to identify all SUs they are assigned to. The carer may ask the researcher any questions they wish about the study.

- Service Users

Each SU will be approached by the researcher, provided with an information sheet about the study, and asked to provide their consent to participate. Again, the SUs can ask any questions they have about the study and may discuss this with their carer, family and friends if they wish. If they do not wish to participate in the study, this will not affect the care they receive in any way. If they would like to participate but are unable to complete questionnaires due to physical difficulties, the researcher can help them by reading the questions and by noting their own responses if required. If they are unable to provide the researcher with consent due to cognitive difficulties, assent will be sought from their assigned consultee.

In this case, the consultee will be provided with an information sheet and asked to provide assent for their SU's participation in the study. If they are agreeable, the SU will be entered into the study.

- Frequent Visitors

When available, the most frequently visiting relative or friend of the consented/assented SU will be approached by the researcher, provided with an information sheet, and asked to provide their consent to participate in the study. If they wish to participate, it will then be possible to gather triad data for this SU (i.e. from SU, carer and frequent visitor). If the visitor does not wish to participate, it will only be possible to gather dyad data for this SU (i.e. from SU and carer).

The frequent visitor will also be asked to provide details on the nature of their relationship to the SU (e.g. sister, brother, daughter, son, grandchild, friend, etc) and the frequency of their visits (e.g. number of visits weekly/monthly/annually).

17.4.4 Procedures

17.4.4.1 Assessments

- Self-Reported EQ-5Ds from Service Users

Consented SUs will be asked to complete the EQ-5D+C (a standard EQ-5D with one additional question for self-reported cognitive ability) with explanation from an independent researcher. The researcher will spend up to 10 minutes to gain a response from the subject. If their attempt proves unsuccessful, the subject will be categorised as unable to participate on that occasion and an explanation will be recorded by the researcher. These participants will be able to participate on another day if they wish, but will remain categorised as initially unable to participate.

If the SU is able to provide responses to the EQ-5D+C on this occasion, they will also be asked to complete the Mini-Mental State Examination (MMSE) by the researcher.

- Proxy EQ-5Ds from Carers and Frequent Visitors

If possible, on the same day, the carer [and most frequent visitor, if available on-site] will be asked to complete two versions of the EQ-5D proxy questionnaire: (i) how the proxy would rate the SU's health (EQ-5D: 1) and (ii) how the proxy thinks the SU would rate his/her own health (EQ-5D: 2). If the visitor is unavailable in person on that day, the researcher will attempt to contact them by telephone. The time between gathering data from each diad/triad should be kept to a minimum (max. 3 days). Proxies will be asked to respond retrospectively so that all EQ-5D reports refer to an SU's HRQoL at the same point in time.

Proxies will also be asked for a simple assessment of the SU's ability to complete the EQ-5D in the form of a 'yes/no' response.

- Researcher Assessment of Cognitive Functioning

In addition to cognitive assessments of the SU, carer and frequent visitor, the researcher will also be asked to provide their own assessment of the SU's ability to complete EQ-5D on the day in the form of a 'yes/no' response.

17.4.5 Sample size

There is no predetermined sample size, although the aim is to recruit as many SUs as possible from two of the larger residential care homes involved in the PAAD study, and their associated carers and frequent visitors. This sub-study may, therefore, include SUs who are not involved in the PAAD Randomised Controlled Study, but aims to include SUs with a broad range of cognitive functioning.

17.4.6 Analysis

Given the relatively small sample and the exploratory nature of this sub-study, the results will be used to generate hypotheses rather than test them.

Agreement in overall EQ-5D scores between proxies and the SU will be assessed using the Bland/Altman method to estimate 95% limits of agreement.

As data on the individual EQ-5D dimensions are trichotomous (score = 1, 2 or 3) we will use a Kappa statistic to examine agreement between scores obtained from a relative and carer for both SU/proxy on each dimension.

We will also use a Kappa statistic to examine agreement between the carer, research nurse and SU's assessment of the SUs cognitive ability on the day and, via ANOVA, will explore differences between the average MMSE scores and those who said 'yes' or 'no' regarding the SU's level of cognitive ability.

While disagreement between responses by any subject and his/her proxies can clearly be due to factors other than cognitive impairment, it is still anticipated that on average, the level of agreement in each of the above analyses will get closer to the level of agreement for a 'clearly cognitively competent' sub-group alone. These results will allow exploration of the MMSE score below which EQ-5D data should be collected by proxy in the RCT.

Ethics approval

This sub-study is classified as a substantial amendment to the main PAAD study.

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19 Appendices

Appendix 1: Bristol Stool Chart

Appendix 2: Example Contacts list of all site personnel working on the Study

Appendix 3: Example PAAD Study Signature list and delegation of responsibilities

Appendix 4:List of Sub study 3 related documents

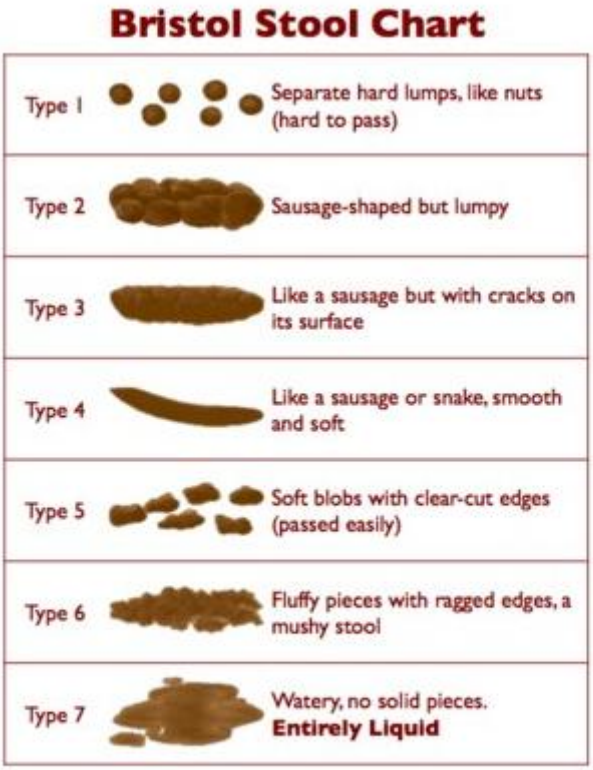
Appendix 5: PAAD Sub-study 2 – Observational CRF

Appendix 6 - List of Documents related to Sub-study 2 :

Appendix 7 - List of Documents related to SubStudy 4:

Appendix 8 - PAAD sub-study 4 protocol – Flow Diagram

Appendix 1: Bristol Stool Chart



Developed by Heaton and Lewis at the University of Bristol

Appendix 2, Example Contacts list of all site personnel working on the Study

PAAD CONTACT DETAILS FOR ALL STUDY PERSONNEL

Care Home			
Address		**Main Contact**	

- Complete this form for all Study personnel
- Notify Arun Acharjya (acharjyaa@cf.ac.uk) of any contact or study personnel changes

	Study Lead (1)	**Study Lead (2)**
Job title		
Name (title, first name/ surname)		
Phone		
Fax		
E-mail		
Address (if different to above)		

	Study Lead (3)	**Care Home Staff**
Job title		
Name (title, first name/ surname)		
Phone		
Fax		
E-mail		
Address (if different to above)		

	Care Home Staff	**Care Home Staff**
Job title		
Name (title, first name/ surname)		
Phone		
Fax		
E-mail		
Address (if different to above)		

Appendix 3: Example PAAD Study Signature list and delegation of responsibilities

South East Wales Trials Unit
Uned Ymchwil De-ddwyrain Cymru

PAAD Study Signature list and delegation of responsibilities

NAME OF CARE HOME:

This form must be completed by all personnel managing Service Users and those responsible for handling & completing Study documentation (e.g. Care Home Manager, Matron, Nurse, general staff). Only staff who are included on this form will be authorised to sign Study forms/CRFs.

Name	Job title/Study role	Sample signature	Sample short Sign. (initials)	Duration From	Duration To	Responsibilities (Please tick all applicable boxes) A	B	C	D	E	F	G	H	I	J

When changes to study personnel occur, please notify the Arun Acahrajya (acharjyaa@cf.ac.uk) by updating this form

Responsibilities key:
A Care of Service Users
B: Site File Maintanance
C: Informed consent & Assessing capacity
D: Notifying next of kin
E: Notifying GP
F: Registration
G: CRF completion
H: SAE reporting
I: Stool sampling

Appendix 4: List of sub study 3 documents

Information sheet for staff
Information sheet for relatives
Information sheet for service users
Information sheet for GPs
Consent form for staff
Consent form for relatives
Consent form for service users
Consent form for GPs
Focus group schedule for staff
Focus group schedule for relatives
Interview schedule for service users
Interview schedule for GPs
Letter of invitation for GPs

Appendix 5 - Observational CRF

Name of care home……..

Name of observer……..

Date:…… Time of observation…….

Domain	Sample topics	Observations	Time
Food and drink	• Time of meals • Staff present • Location of meals (any taken in bedrooms) • Any medicines given at mealtimes • Assistance given with feeding • PEG feeding • Tea/coffee times (and where given)		
Medication / drug dispensing	• Time of day • Who gives medication • Recording of medication giving • Delivery of medication • Location of Mars sheets		
Toileting	• Private or communal toilet • Mobile SU • Immobile SU		

	• Who assists with toileting • Recording of bowel habits (where/when) • Record for each service user?		
Administration	• Visiting times (popular and less popular times) • Visiting arrangements • Record keeping (where, how, who) • Staff mix • Staff breaks and meal times		
Communication	• Shift handover (how done, what said, who participates) • Information given to junior staff • Information given to relatives		
Other activities	• Quiet periods • Social activities • Therapy		
Other events	• Incidents (hospitalisations, falls, etc how dealt with) • Visits from GP		

Other comments and notes:…(including staff reflection on whether it's a normal day)

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Appendix 6 - List of Documents related to Sub-study 2 :

Care Home letter Invite Version 1.0 dated 30/07/2011

Appendix 7 - List of Documents related to SubStudy 4:

Consent for Carer, Version 1.0, dated 30/07/2011
Consent form for Consultee, Version1.0, dated 30/07/2011
Consent form for Realative/friend, Version 1.0, dated 30/07/2011
Consent Form for Service User, Version 1.0, dated 30/07/2011
Information Sheet for Carer, Version 1.0, dated 30/07/2011
Information Sheet for Consultee, Version 1.0, dated 30/07/2011
Information Sheet for Realtive/Friend, Version 1.0, dated 30/07/2011
Information Sheet for Service User, Versiuon 1.0, dated 30/07/2011
Pictorial Summary Sheet for Service Users, Version 1.0, dated 30/07/2011
Summary Sheet for Service Users, Version 1.0, dated 30/07/2011

Appendix 8 - PAAD sub-study 4 protocol – Flow Diagram

- Note: **DIAD** = Service user and Carer. **TRIAD** = Service user, Carer and Frequent Visitor (Relative/Friend)