Community IntraVenous Antibiotic Study (CIVAS): Evaluation of Patient Preferences for and Cost effectiveness of Community Intravenous Antibiotic Services

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Title: Evaluation of Patient Preferences for and Cost effectiveness of Community Intravenous Antibiotic Services

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Abbreviations/acronyms

BSAC	British Society for Antimicrobial Chemotherapy
CEAC	Cost Effectiveness Acceptability Curve
DCE	Discrete Choice Experiment
ICER	Incremental Cost-effectiveness Ratio
IV	Intravenous
NICE	National Institute for Health and Clinical Excellence
OPAT	Outpatient Parenteral Antimicrobial Therapy
PAG	Patient Advisory Group
QALY	Quality-Adjusted Life Year

1 Summary

In the UK there is patchy implementation and significant variation in community IV antibiotic services geographically. This is despite the potential community IV services have for cost reduction and increased patient choice and satisfaction. There is a paucity of information upon which the NHS can base decisions regarding the design, supply and commissioning of such services and upon which national guidance developers can base recommendations for best practice. The proposed research would address significant gaps in knowledge about the cost-effectiveness of different IV antibiotic service models, and identify which services patients prefer and which aspects of the services are most important to them. The evidence generated by the research would be used to help identify the optimal configuration of services in terms of value for money and patient preference. The research would also help identify future research priorities and help design clinical studies that would generate the evidence necessary to aid decisions over service provision.

2 Background

Delivery of IV antibiotics to patients outside a hospital setting – often termed Outpatient Parenteral Antimicrobial Therapy (OPAT) - was first described on a small scale in the 1970s in North America. By the end of the 1990s an estimated quarter of a million patients annually were receiving IV antibiotics on an outpatient basis due to cost savings, patient preference, better IV devices, the introduction of antimicrobial agents which only needed administration once or twice a day and the development of dedicated service providers. A wide variety of infections have been treated through this system, in particular skin and soft tissue infections, but also bone and joint infections, bacteraemia, wound infections, pneumonia, complicated urinary tract infection, intra-abdominal infections, device related infections, endocarditis, and central nervous system infections. Although widely accepted as the standard of care in countries such as the USA and Australia, such services are largely limited to patients with appropriate health insurance cover (Paladino and Portez, 2010).

2.1 Clinical practice in the UK

In recent years OPAT services have been developed in some areas of the UK both in the NHS and private sectors, in response to local pressures in combination with health care staff initiatives (Torok et al., 2010). This has led to many service variations using different heath care professional groups which can be grouped into four main categories:

i. Outpatient attendance at healthcare facility

A variety of NHS hospital departments have set up systems for providing IV antibiotics for patients attending on a daily basis, including both specialist and general services. The main disadvantage to this system is the inconvenience to the patient in having to travel, the fact that it is limited to patients fit to travel and the cost of transport.

ii. Self-administration of IV antibiotics

Particularly where patients require very long or repeated courses of antibiotics, patients or carers have been taught to self administer the treatment. This system is likely to be cheaper in that less professional time is required once the patient has been trained but there are potential risks to unsupervised administration, including non-compliance.

iii. Visiting general nurse model

There are instances of NHS community nurses (e.g. district nurses) administering IV antibiotics; this can be efficient as they can perform other tasks such as wound management at the same visit and with minimal travelling as they are based locally. However, they are likely to be less confident and skilled in IV antibiotic management as this makes up a small percentage of their work and they may have insufficient time to add this to their caseload.

iv. Visiting specialised nurse

In contrast, specialised visiting nurses have more expertise but may be less efficient as they cover a large geographical area. This is the main model of care in the USA, and is generally provided by private specialised companies. In the UK this model is available through a few providers, both private sector and NHS but there is little data on how frequently they are utilised.

2.2 Summary of published evidence

Scoping literature searches show approximately 500 published papers in this field. Clinical efficacy and safety has been addressed in many different clinical areas and using a variety of models of care, largely using retrospective analysis of single centre experience (Kiernan et al., 2009, Mackintosh et al., 2011, Nazarko, 2008, Yan et al., 2011). Some risks of community based IV therapy have been identified and projects initiated to minimise these (Gilchrist et al., 2008). The potential for treatment of micro-organisms resistant to antimicrobials and in limiting the spread of health-care associated infection has been high-lighted as an OPAT benefit (Torok et al., 2010). Newer antimicrobial agents have been assessed for their potential for OPAT use usually because they have long half-lives with less frequent dosing required and may be effective against resistant micro-organisms such as MRSA (Bazaz et al., 2010, Tice and Rehm, 2010). However, such agents are much more expensive so increase the cost of the service. There have been evaluations of the staff required to provide such services. However, the conclusions of such studies vary with the benefits of a nurse-led service (Seaton et al., 2005) and the need for infection

specialists (Sharma et al., 2005) both being suggested. There is a striking lack of prospective studies, and only one randomised controlled trial which was conducted in New Zealand (Corwin et al., 2005).

While health economics have been addressed in depth overseas (especially the USA) there is little detailed analysis in the UK. Most economic evidence comes from studies reporting bed days saved and simple analyses of cost savings – which are reported to be significant. According to one recent review, a comprehensive pharmacoeconomic evaluation of OPAT services has yet to be completed despite the number of published studies (Paladino and Portez, 2010). Chapman and colleagues (Chapman et al., 2009) did complete a cost-effectiveness analysis of OPAT in a UK setting but this included only one centre and was predominantly a comparison of standard hospital inpatient care with daily attendance at a hospital facility In addition, due to a lack of appropriate data, the analysis completed was a cost-consequence analysis rather than a cost-utility analysis and thus did not adhere to the NICE reference case. Little has been published on patients' preferences for different services, although reports of patient satisfaction with services have been cited. Only one study was found to evaluate patient preferences directly in this group, finding 90% of patients preferred treatment at home to treatment in hospital (Marra et al., 2005). However, this study was conducted in Canada, had a small sample (n=71), only compared two fixed-service models (in hospital vs self-administration at home with weekly hospital visits) and used willingness-to-pay to measure preferences.

2.3 National policy and current research

Following a conference on OPAT in 2009 hosted by the British Society of Antimicrobial Chemotherapy (BSAC), a UK database is being introduced where centres have the option of sharing their data on, for example, service type, patient numbers and outcomes. A voluntary survey of existing services provided by OPAT group members was carried out at the end of 2011 and the data obtained is currently being analysed in preparation for publication. The BSAC sponsored OPAT project is supporting the development of such services throughout the UK without favouring any particular model of service design. Various resources have been provided to facilitate this including development of practice standards, a preceptorship scheme, regional training days, a model business case including 'SWOT' analysis of service models, and software to support a virtual ward round (http://e-opat-com/) As yet no national policy in this area exists although we understand that there have been meetings between members of the OPAT scheme steering group and the Department of Health in March 2010 regarding further service development.

2.4 Need for the research

OPAT services have the potential to generate significant cost savings for the NHS and deliver greater patient satisfaction. They may contribute to the delivery of key healthcare strategies and directives such as Equity and Excellence: Liberating the NHS (2010), Creating a Patient-led NHS (2005) and Your Health, Your Care, Your Say (2006). However, the full potential of OPAT has not yet been realised in the UK as there is patchy implementation and significant variation in services geographically. There is a paucity of information upon which the NHS can base decisions regarding the design, supply and commissioning of such services and upon which national guidance developers can base recommendations for best practice.

The proposed research would address significant gaps in knowledge about the cost-effectiveness of different IV antibiotic services; identify which services patients prefer and which aspects of the services are most important to them. Since the services available to patients have different costs, effects and risks it is essential to understand what patients consider most important in the care they receive and what trade-offs they are willing to make. This is especially so assuming the trend for enhancing patient choice continues in the NHS. The optimal delivery of OPAT may mean offering patients a choice between several services concurrently which has consequences for future planning and resourcing. The evidence generated by the research would be used to help identify the optimal configuration of services in terms of value for money and patient preference. The research would also help identify future research priorities and help design clinical studies that would generate the evidence necessary to aid decisions over service provision.

3 Aims and Objectives:

The aim of this research project is to: establish the types of intravenous (IV) antibiotics services available in England and identify barriers to the use of each service type; evaluate patients' preferences for, and the costs and benefits of, delivering IV antibiotics in the community; make recommendations for the optimal delivery of the service and for the design of future clinical trials. IV antibiotic services have significant potential for cutting NHS costs and for improving patient choice and satisfaction. The research will help identify which aspects of services and service types are the most preferred and which offer the greatest benefit to patients and the NHS in general.

3.1 Primary objectives:

a) Evaluation of the existing evidence of efficacy, safety and cost-effectiveness of different IV antibiotic services

b) Assessment of current OPAT provision by the NHS, establishing reasons for current service configuration and identifying barriers to service provision

c) Economic modelling of the different delivery systems to evaluate their cost-effectiveness in both short-term and longer-term infection patient groups

d) Determination of patient preferences for different community IV antibiotic service attributes through a discrete choice experiment

e) Hold an expert panel workshop to agree on what may constitute the optimal service model of community IV antibiotics delivery and how future clinical trials should be designed to test these services

4 Study Design

4.1 Summary:

The Study will use a mixed methods approach, combining qualitative and quantitative techniques to comprehensively evaluate current OPAT provision in the NHS. It will be evaluated in terms of efficacy, cost effectiveness and patient preferences for service delivery. The methodology is broken down into 5 work streams. Ethical approval is requested for work package 2 to 4 which are described below. Each study is described in detail (design, outcomes, recruitment/sampling and analysis). Information on work package 1 and 5 is provided for information only (University ethical approval is being sought for work package 2).

Work Package 1:

Systematic Review: To establish published research on the safety, efficacy and cost-effectiveness of community IV antibiotic delivery services (ethical approval not requested for this work package and information is provided for background only)

Work Package 2:

Qualitative Study: National electronic survey directed at NHS Acute Trusts across England and semi-structured telephone interviews with 30 OPAT service managers across the UK to explore models of service offered and establish why they provide the service models they do and to identify perceived barriers to the provision of other services.

Work Package 3:

Health Economics Cost Effectiveness Study: To assess the relative cost-effectiveness of service models. The economic model will estimate the comparative value of four different community IV antibiotic services and allow comparisons of the expected costs and benefits of each service for both short-term and longer infection patient groups. The evaluation will also model the costs and benefits of running several services concurrently and providing patients with a choice between them.

Work Package 4:

Discrete Choice Experiment (DCE): To determine patient preferences for different methods of IV antibiotic service. The study will use discrete choice methodology to inform us which aspects of treatment are important to patients and which they would prefer in the future. Two groups of patients will be included; patients with skin and soft tissue infections which usually require less than a week of treatment (e.g. cellulitis) and patients who have deeper infections which generally require much longer treatment courses (e.g. bone infections).

Work Package 5:

Expert workshop and panel: To agree which service models are worthy of testing in clinical trials and to discuss trial design issues.

Our patient advisory group (PAG) will be involved in each of the work packages (see PPI Section for details)

Work packages 1-4 will be discrete research projects, conducted independently. However, knowledge and information from each will feed into and inform the other work streams with some tasks being conducted in parallel. The information and evidence from work packages 1-4 will then be presented to, and considered by, a group of patients and clinical and research experts who will reach a consensus on which models of care likely represent the best value for money, deliver the greatest patient satisfaction and therefore considered worthy of evaluation in a clinical trial. Initially the service models under consideration will be:

i. Outpatient attendance at healthcare facility

ii. Self-administration of IV antibiotics

iii. Visiting general nurse model

iv. Visiting specialised nurse

However, this may change in light of responses from the national survey of service provision and manager telephone interviews.

The analyses will require a comparison of two main groups of patients: those with short-term, skin and soft tissue infections, and those with more deep-seated, complex and, consequently, longer-term infections. Since the treatments, treatment delivery systems and treatment durations can be quite different for these patients, it is important that they are considered separately.

5 Setting

The study will be conducted in 4 NHS Acute Trusts in West Yorkshire.

Leeds Teaching Hospitals NHS Trust

Bradford Teaching Hospitals NHS Foundation Trust

Mid Yorkshire Hospitals NHS Trust

Calderdale and Huddersfield MHS Foundation Trust

6 Detailed Methodology

6.1 Work Package 1: Systematic Review

To establish published research on the safety, efficacy and cost-effectiveness of community IV antibiotic delivery services (ethical approval not requested for this work package and information is provided for background only)

The review and synthesis of data will be undertaken in accordance with the Centre for Reviews and Dissemination guidelines for systematic reviews [22]. A protocol of the review, including proposed search databases, search terms, inclusion/exclusion

criteria and data extraction forms will be produced for review prior to the systematic review commencing. The final protocol will be added to the PROSPERO database (http://www.crd.york.ac.uk/prospero/, 2012). The databases to be searched will include general medical databases such as Medline and Embase, nursing databases such as Cumulative Index to Nursing and Allied Health Literature, evidence libraries and economic databases such as NHS Economic Evaluation Database. Further potentially relevant studies will be identified by scrutinising the reference lists of selected/included studies.

We expect that there will be few qualitative studies and the use of a highly structured search strategy may miss potentially relevant papers and so to we will use Critical Interpretive Synthesis developed by Dixon- Woods et al (2006) to review and analyse the qualitative literature, which draws on aspects of meta-ethnography and grounded theory (Glaser and Strauss, 1967), in particular, the use of constant comparative analysis. In this approach, searching, sampling and critique goes on in parallel to develop a coherent theoretical framework. Ongoing selection of potentially relevant literature will be informed by the emerging theoretical framework. This may include literatures not directly relevant to the question under review. For example, we may explore 'models of care literature' from other health care areas. The output will be a narrative presentation of the results which will identify key constructs important to patients and staff. The synthesis of qualitative literature will focus on developing an understanding of the appropriateness and the acceptability of OPAT services from the perspectives of the patients requiring treatment and staff delivering their care.

The quality of studies reporting economic evaluations will be assessed using the Drummond and colleagues checklist (Drummond et al., 2005). Studies will be selected by two researchers working independently with inconsistencies resolved following discussion. Review data will be synthesised and provide values for use in the economic model, DCE and evidence for consideration by the expert panel. The literature review will be completed by month six of the project. Considering the length of the study period the review will be updated toward the end of the economic modelling to ensure that the most up to date information is captured.

Our Patient Advisory Group (PAG) will be involved in developing the protocol and reviewing the findings of the literature review.

6.2 Work Package 2: Qualitative Study:

Electronic survey of Infection specialists and interviews with OPAT service managers across the UK to establish why they provide the service models they do and to identify perceived barriers to the provision of other services. (University Ethical approval applied for).

Rationale:
The proposed research aims to identify the most cost-effective and most-preferred models of service. However, it is also important to ascertain the types and levels of current service provision in the UK, whether variations in provision exist and possible causes of variation. We will therefore explore whether barriers exist to the provision of particular services (or range of services). This work package will help establish which service models are feasible and which service can be considered 'standard care' in the economic model.

Design: Qualitative telephone interviews.
Initially a brief electronic or telephone survey will be administered to infection unit managers and/or infection specialists to establish types of services available in England. A number of units will be purposively sampled from those who completed the survey for the telephone interviews. The number of OPAT sites and budget constraints necessitate a broad, 'Framework' approach. Framework analysis is useful for a structured exploration of participants' perspectives and provides an advantage because findings are induced from their original accounts (Ritchie and Lewis, 2003). This approach provides less detail than other approaches (e.g. Grounded Theory), but it will enable us to gather data from a range of service providers, and understand the barriers and facilitators (personal (e.g. attitudinal), geographical, resource (e.g. staffing), organisational and policy issues (e.g. commissioning decisions)) that influence service delivery and potential ways to circumvent these implementation barriers.

Sampling:
Purposive sampling via sampling matrix will recruit participants with different experiences of delivering OPAT services. A sample of n=30 infection specialists and/or unit managers will be recruited. Our intention is to capture a detailed and comprehensive range of perspectives and participants will be identified using a pre-determined sampling frame using the following characteristics: NHS Trust Type (Teaching, Foundation Trust, District General Hospital); Geographical area (urban and rural); Socio-economic area (low and high SES); Diverse ethnicity. Some selection criteria are likely to be nested (e.g. hospital type, geographical area) and care will be taken to ensure that all viewpoints are represented.

Data collection:
Semi-structured, telephone interviews. Interviews will follow a topic guide that will be developed from the literature review and expert opinion (clinician co-applicants/advisors and PPI members). The researcher will probe pertinent initial responses and expand on issues raised. Interviews will be recorded and transcribed verbatim.

Data analysis:
The guiding approach will be Framework Analysis (Ritchie and Lewis, 2003). Data analysis will comprise five stages: i) familiarisation with the data; ii) identifying the thematic framework; iii) indexing; iv) charting; and, v) mapping and interpreting. The process of familiarisation enables the researcher to identify emerging themes or issues in the data. Little is known about why NHS Trusts choose to deliver specific

OPAT models and so the evidence generated from the literature review and input from our clinical co-applicants will be used to help refine the thematic framework (Identifying the thematic framework). All of the data generated from the interviews will be indexed numerically according to the particular theme to which it corresponds (Indexing). Data will then be lifted from its original text and placed under subheadings derived from the framework (Charting).The analysis of the concepts identified in early interviews will inform revisions to the interview guides for subsequent interviews (Interpretation).The themes are flexible and can be modified in the light of new data, and a process of constant comparison will be used to examine across themes and cases. The goal of our analysis will be to develop a better understanding of the models of service delivery offered across the UK, the rationale for service delivery decisions, the barriers to particular service models and facilitators of change. These interview data will be considered by the expert panel and inform the modelling and DCE work streams.

6.3 Work Package 3: Health Economics Cost Effectiveness Study: To assess the relative cost-effectiveness of service models.

Rationale:
The economic model will estimate the comparative value of (it is assumed) four different community IV antibiotic services and allow comparisons of the expected costs and benefits of each service for both short-term and longer infection patient groups. The evaluation will also model the costs and benefits of running several services concurrently and providing patients with a choice between them.

Design: Economic Model
The analysis will conform to the reference case set out by the National Institute for Health and Clinical Excellence (NICE, 2008). As such, the economic analysis will be a cost-utility analysis (CUA) between service models and effectiveness measured in terms of quality-adjusted life years (QALYs). It is quite possible that the relative benefits of the service models may not register in terms of QALY gains (especially for short-term infections where treatment may last only one week). As a consequence, we will also conduct a CEA based on cost per patient successfully treated. The analysis will take the perspective of the service provider including the costs of health and social care, although a secondary analysis will take the societal perspective taking into account, for example, patient and caregiver out-of-pocket costs and productivity loss. Currently the daily hospital treatment service will be considered ‘standard care’ for the analysis but this may change in light of the survey and interviews of infection unit managers/specialists.

Sample/Data:
The data for the analysis will come from existing published sources and from surveys. The economic analysis will require data from 400 participants. We will use

the same sample as the discrete choice study (see below) (n=200) but we will also need to recruit an additional 200 patients to provide data to inform the modelling. Final numbers will be influenced by the outcome of the survey. If we need to look at additional models of care, over and above the four currently identified, we will need to collect data on up to an additional 100 participants. As certain models of care are used less frequently (in particular self- or carer- administration) if necessary we will look for further sites using such models using information from our Health Professional Survey and through the NIHR Infectious Diseases and Microbiology Specialty Group in order to obtain the necessary numbers.

Data Collection:
Data (e.g. NHS resource use and costs, treatment efficacy, event and risk probabilities and utility values) for the economic model will be derived from the literature review, from the DCE interviews, from retrospective investigation of hospital and GP records and from clinical experts. We will also seek access to the British Society of Antimicrobial Chemotherapy (BSAC) database which includes outcomes data. Patients' use of NHS resources will be captured in two ways: indirectly from medical records and directly from patient reports of service use. The research nurse will be responsible for visiting participating hospital sites and extracting historic data for IV patients (with patient consent). Specifically, data will be collected on treatments received and their effectiveness, their duration and location, treatment delivery systems, additional health services used or visits required and adverse events. Practice staff working at participating GP surgeries will perform a similar task, supported by the Primary Care Research Network. The research team have devised a data collection form to facilitate uniform and complete data capture (see supporting documents). All data will be anonymised.

Patients participating in the DCE (see below) will also be asked to complete a utility questionnaire and resource use questionnaire, with the latter asking about services used as a result of their infection. Costs and outcomes (in terms of healing time and adverse events) will be collected from centres representing the four models of OPAT delivery that are being compared. If we have insufficient data on particular parameters we may convene a clinical expert and patient consensus panel to agree on suitable model values.

Unit costs for treatments, health service staff and resources will be obtained from national sources such as the Personal Social Services Research Unit (PSSRU), the British National Formulary (BNF) and NHS Reference cost database. Where national unit costs are not available the finance departments of trusts participating in the study will be asked to provide local cost data. Health state utility values for the CUA will come primarily from patients participating in the DCE who will complete an EQ-5D [25] questionnaire, which is NICE's preferred source of utility values. The EQ-5D is a simple, five item questionnaire which provides utility values based on a UK general population-derived tariff. We will also include a generic utility measure such

as the ICE-CAP as this may represent a broader measure of patient benefit and capture aspects not included in the EQ-5D. We will also use health state utility values identified in the literature if appropriate.

Sample size:
Standard sample size calculations do not apply as the CUA will combine information (both aggregate and patient level) from several sources. However for the patient level data, as we have effectively two patient groups and assuming four service models, there are eight (2 x 4) sample cells to fill. We aim to ensure that cost and outcome data will be available for 50 cases in each cell to give robust estimates; this means that 400 data records are required. However, since cost and outcome data will come from 200 patients completing the DCE, we will only therefore require the retrieval of 200 data records (see note above on sample size). Should the BSAC registry database be made available we will have access to significantly more outcomes data.

Data analysis:
The CUA will compare the three models of community IV antibiotic service delivery to daily hospital attendance (considered 'standard care'). A Markov decision model will be developed which – based on input from PAG members and clinicians – will describe the patient pathway and potential outcomes and provide estimations of expected costs and benefits for the service models. Published best practices will be employed to develop and test the model (Caro et al., 2012). We will adhere to NICE technology appraisal guide and subsequent Technical Support Documents produced by the NICE Decision Support Unit in identifying and selecting parameters (Kaltenthaler et al., 2011). If costs are greater and comparison interventions more effective or if the interventions are cheaper and less effective, results will be presented as expected incremental cost effectiveness ratio (ICERs), expected net benefit (assuming lambda is equal to the NICE QALY threshold of £20,000) and a cost effectiveness acceptability curve (CEAC)(Fenwick et al., 2001). QALYs will be based on EQ-5D utility values although estimates for other health states that may be required in the model (e.g. for hospitalisation or hospital-acquired infections) may come from direct values (such as time-trade off) found in the literature. Markov health states (e.g. 'infected', 'cured', 'hospitalised') will have costs and utility values associated with them and the modelled patient cohort will accrue or lose utility (or health related quality of life) as they move between the states.

Although separate analyses will be conducted for the short-term and long-term infection patients, further sub-group analyses by diagnosis may be possible depending on the sample sizes available. Uncertainty analysis will be undertaken using non-parametric bootstrap simulation. In addition, probabilistic sensitivity analysis will be undertaken to test the robustness of the results to parameter uncertainty. Monte Carlo simulations will be conducted to determine the effect of input parameter variation on the CEA results. We will use the value of information

framework to explicitly quantify the implications of decision uncertainty. We will calculate the expected value of perfect information (EVPI)(Brennan and Kharroubi, 2007) to help determine the value of, and priorities for, future research and the expected value of sample information (EVSI) to design efficient future research. This information will be used by the team and trialist to help plan future clinical trials.

6.4 Work Package 4: Discrete Choice Experiment (DCE): To determine patient preferences for different methods of IV antibiotic service.

The study will use discrete choice methodology to inform us which aspects of treatment are important to patients and which they would prefer in the future. Two groups of patients will be included; patients with skin and soft tissue infections who usually require treatment for less than a week and patients who have deeper infections which generally require longer treatment courses.

Rationale and Theoretical Framework:

A core aim of the study is to understand patient preferences for different methods of IV antibiotic delivery. While initial insights into overall preferences can be obtained by direct questioning as to which method a given patient prefers, such approaches fail to recognise that the actual preferences will be a function of the detailed characteristics of the specific delivery methods. In particular, they will be the result of trade-offs, where a patient selects the option that provides the best overall combination of characteristics. In the context of the present study, such trade-offs may for example arise when a patient feels that receiving the IV treatment as an out-patient may involve more highly qualified staff, but be more inconvenient because they have to travel to hospital and also have the added risk of hospital acquired infections. The quantitative study of such choices involves the use of discrete choice models, which are mathematical structures belonging to the family of random utility models (see Train, 2009 for a comprehensive overview). A substantial number of studies in health economics now make use of choice modelling techniques(de Bekker-Grob et al., 2010) and our methodology will follow best practice established therein (Lancsar and Louviere, 2008). Attribute development for the DCE will be conducted in two phases (conceptual development and refinement of terms used) using recommendations by Coast et al.(2011). This will be followed by the development and piloting of the interview following recommendations by Willis (2005). Information from the literature review and record retrieval (for example on treatment effectiveness) will also inform survey content. Our PAG will be closely involved with this work package, providing input into the development of study materials (e.g. DCE items) and interpretation of interview data. They will also provide a patient perspective on the interpretation of the resulting models.

6.4.1 Phase 1 (Attribute development)

Overview: Qualitative study using focus groups and in-depth semi-structured interviews to ascertain service issues of importance to patients that will be included in the DCE survey. Two discrete groups of patients will be recruited (short-term antibiotic patients and longer-term antibiotic patients), with conventional content analysis of focus group and interview data (Hsieh and Shannon, 2005).

Design: Qualitative exploration of patient's experiences of receiving IV antibiotic services and their views on the important aspects of the service.

Qualitative research is useful where there is little known on a topic and a brief scoping search revealed little qualitative literature in this area. The use of primary qualitative data to inform the development of discrete choice experiments is quite new and we will follow guidance developed by Coast et al (2011) to inform this work. We will use constant comparative methods; a method derived from Grounded Theory, with data collection and analysis proceeding concurrently (Hsieh and Shannon, 2005). New codes will be developed from data to build up an understanding of informants' experiences of IV antibiotic services, knowledge of treatments, effectiveness and acceptability and accessibility of services (location, provider, options for care etc.). As West Yorkshire parallels the demographics of other UK areas with areas of high and low deprivation, ethnic diversity and a mix of rural and urban populations the results of our qualitative data analysis should be highly informative and provide the breadth needed for the development of the DCE attributes.

Sample:

Participants aged over 18 years, who have experienced IV antibiotic treatment. We will recruit from 6 sites (Bradford, Calderdale,Leeds and Mid-Yorkshire Acute Trusts). We will purposively sample via a sampling matrix to recruit for diversity of experience (to reflect variation in age, gender, socio-economic status, ethnic background, illness/condition, antibiotic experience, geographic area) to ensure we include patients who have experience of a range of IV antibiotic services. Sample: Two groups of participants will be recruited: a) patients requiring short term IV antibiotics (n=15 participants) and b) patients who have had deep-seated infections requiring longer term IV antibiotics (n=25 participants). The estimated sample is based on previous studies (for a review see Coast et al., 2011) and assumes those on longer term antibiotics will be a more diverse population. It is our intention to capture a detailed and comprehensive range of perspectives and recruitment will continue until there is no new variation in observations (data saturation). However, the use of interviews to develop DCE experiments is relatively new, so final numbers will be determined when data saturation is reached, and is likely to be affected by the proportion of participants choosing to be interviewed, rather than attending a focus group.

Data Collection - Interviews and Focus Groups:

Two methods of data collection will be used to help develop the DCE attributes. Focus groups will be offered to participants as these create a space for people to present their ideas and experiences, but also to generate new ideas. However, we are aware that some people will be of working age and less able to attend a focus group, and some older people may struggle with a focus group setting because of pre-existing conditions (e.g. frailty, deafness), and so to maximize recruitment we will be flexible in our approach, with interviews offered to those unable/reluctant to attend a focus group. For both the focus groups and interviews, the researcher will use a topic guide (draft enclosed as supporting document) that will be informed by the literature, with input from our PAG and clinical experts. The researcher will probe pertinent issues with participants and expand on issues raised. Interviews will take place at a venue of participants' choice (NHS, university or participants' home). Focus groups will take place at venues across West Yorkshire (likely to be held on NHS host sites and university premises) to give participants the opportunity to attend a session closer to their home. All sessions will be recorded and transcribed verbatim. Focus groups will be of a standard size to allow discussion (n=5-8 participants) and will be facilitated by experienced researchers. Interviews and focus groups will be largely semi-structured in a format to ensure that the four identified service models are discussed. Time will also be scheduled for participants to suggest alternative service attributes and models for which they have a preference. This will ensure that patients have the freedom to highlight and discuss the aspects/attributes of OPAT care that are important to them regardless of whether or not those attributes exist in currently provided service models. We also ask the participants to think about their attitudes to community IV delivery and the NHS in general.

Data analysis:

The principle approach will be content analysis, with data analysed for patterns and themes, to develop categories and sub-categories of attributes and arrive at a comprehensive set of attributes. Data will be analysed iteratively using constant comparative methods(Strauss and Corbin, 1990). Data analysis will follow the standard methodology for thematic content analysis; close reading of the data to identify words that capture thoughts or concepts. Labels/codes are attached to these data and become the initial coding frame. Codes are then sorted into categories based on how they relate to one another, and grouped into meaningful clusters. Data will be charted to organise the categories into a meaningful structure and definitions for each code and subcategory developed. The results of the analysis will be used to a) develop vignettes for the DCE which reflect the experiences of participants; b) construct the attributes and levels for the DCE scenarios.

6.4.2 Phase 2 (refinement of terms)

To ensure that the items reflect the experiences of our population we will undertake further testing prior to the main DCE study. We will work with PAG members to refine the language used to describe the attributes identified in Phase 1 and develop draft wording for DCE items. We will then conduct two focus groups to ensure the DCE includes the factors participants consider most important, that the wording of the draft items resonate with participants. Finally, we will pilot the DCE using a 'think aloud' cognitive interviewing technique (Willis, 2005) with a 'naive' sample of participants to examine comprehension, and response processes, to identify problems and limitations of the DCE vignettes and attributes and make final revisions to the vignettes and questions.

Design: Focus groups

Sample:

Participants for the focus groups will be drawn from the sample recruited in Phase 1; one with 5-6 short-term infection patients and one with 5-6 long-term infection patients.

Data collection and analysis:

The procedure described above will be used. The focus groups will be audio recorded and notes made. These data will be used to revise the vignettes and DCE items.

6.4.3 Phase 3: Piloting the DCE

Design: "Think aloud" Interview/pilot study:

The DCE interview will be pilot tested with a group of patients to check their understanding of the task and the relevance and importance of the attributes/levels and to check interview times and response rates. The pilot will include a cognitive debriefing approach where patients are encouraged to 'think aloud' when making their choices. These data will be used to determine whether the DCE is capturing issues of importance in a valid manner and whether revisions are required.

Sample:

Participants aged over 18 years, who have experienced IV antibiotic treatment. We will recruit from 4 sites (Bradford, Calderdale & Huddersfield, Leeds and Mid-Yorkshire Acute Trusts). We will purposively sample via a sampling matrix to recruit for diversity of experience (to reflect variation in age, gender, socio-economic status, ethnic background, illness/condition, antibiotic experience, geographic area) to ensure we include patients who have experience of a range of IV antibiotic services. A total of 30 participants will be recruited.

Data collection:

A cognitive testing protocol will be devised consisting of the draft DCE questionnaire and probe questions to explore how participants understand the DCE vignettes, attributes and levels.

The questionnaire will be administered in a one-to-one interview and participants will be asked to think aloud as they answer the questions and the interviewer will ask supplementary questions to explore the answers provided. With participants' consent, interviews will audio taped and notes made during the interviews.

Analysis:

The notes and recordings will be reviewed after each interview. Each round of testing will comprise 5 interviews. After every five interviews the findings will be reviewed and interpreted and where appropriate changes made to the DCE questionnaires. Following each round of testing, review and modification, the revised questionnaire will be tested in a further round and interview times and response rates checked (Willis, 2005).

6.4.4 DCE (Discrete Choice Experiment)

Sample size:

It is difficult to estimate required sample sizes for DCEs as these depend on the number of choice tasks completed by respondents and the number of attributes and levels presented in each choice. It is thought that n=100 respondents with short-term infections and a further sample of n=100 respondents with longer-term infections should be sufficient to allow determination of robust preference data, especially as we will make use of advanced survey design techniques that maximise the potential for trading between attributes, and hence increasing the information content of the data (Bliemer and Rose, 2009). If, however, we need to add an additional treatment model to the study this sample size will increase.

Sample: Patients will be recruited (as they receive current treatment or retrospectively from records) from each of the sites, who between them provide each of the services under investigation.

Data collection:

The interviews will be carried out by the researcher using a laptop to present the choices to respondents on a one-to-one basis.

DCE Questionnaire:

We propose to conduct two separate main DCE interview surveys (one each for the two patient groups). The actual survey design will differ between the two groups to make the scenarios appropriate to specific patient circumstances. We envisage presenting each respondent with a number (about eight to ten) of different choice scenarios. The differences between the scenarios will be the actual combinations of attributes presented, where these will come from the experimental design.

Although we have four alternatives representing the four main service models, it is possible that we will present only three options at any one time to patients to minimise burden, namely: outpatient attendance at healthcare facility, self-administration of IV antibiotics at home, administration by nurse visiting home. However, in this case we would vary the attributes (and titles i.e. 'Specialist' and 'General') of the nurse visiting home model such that it covers both alternatives. Either way, the design of survey will be such that it will allow us to capture the relative preferences for all four service models. The planned pilot survey will allow us to determine the most appropriate survey design.

Each of these alternatives will be described by a number of attributes to be determined by the qualitative research; these attributes may or may not be currently available in existing service models. In each scenario, the respondent will be asked to indicate his or her preferred option. We will also investigate the scope for collecting a full preference ranking, which would provide enriched data. An example discrete choice task using illustrative attributes is included in the survey as supporting documentation.

A key issue affecting many studies making use of discrete choice data is the risk of bias, either hypothetical or strategic. Hypothetical bias can arise due to differences between the choice task and real world choice contexts (Hensher, 2010). We are confident of mitigating these effects by making use of respondents who can relate to the experiments, namely patients who are (or have previously) undergoing IV antibiotic treatment. The risk of hypothetical bias can be further mitigated by reducing the potential of respondent misunderstanding. This is a key argument of conducting face to face interviews rather than a postal survey. Strategic bias on the other hand can be caused by strong underlying (and often uninformed) preferences, and can also arise if respondents feel that through their choices, they can influence policy decisions (see Lu et al., 2008). Here, we propose to make use of appropriate introductory material, explaining in an unbiased manner the different modes of delivery, and explicitly instructing respondents to make their choices as in real life. We will additionally collect extensive information from respondents relating to underlying attitudes and perceptions. Patients will also complete the EQ-5D, ICE-CAP, resource use and socio-demographic questionnaires and a brief survey asking about their satisfaction with the care they received.

Data analysis:

For the data analysis, we propose to move beyond those types of choice models typically employed in health economics. In particular, we will make use of advanced mixture models that will allow us to accommodate the expected high level of heterogeneity in sensitivities/preferences across individual patients (Hensher and Greene, 2008). We will seek to explain large parts of this heterogeneity by linking sensitivities to patient characteristics, and will also make use of constructs that allow us to explicitly incorporate underlying attitudes (Ben-Akiva et al., 2002). Any remaining unexplained heterogeneity will be accommodated in a random manner. The lead choice modeller SH has extensive expertise in this context (Hess and Beharry-Borg, de Bekker-Grob et al., 2010, Hess et al., 2005), and it is well known

that an appropriate treatment of the various types of heterogeneity is likely to provide more robust overall measures of sensitivities. The components of the model relating to attitudes will also help us to mitigate the effects of any strategic bias that may arise in the data.

6.5 Work Package 5: Expert Panel Workshop

The role of the Expert Panel will be to consider the evidence generated from the literature review, qualitative research, economic modelling, DCE, survey of current service provision, to reach consensus on what is likely to represent optimal community IV antibiotic therapy for the two patient groups (long and short term IV antibiotic patients).

Design:

A consensus workshop to consider the evidence collected in work packages 1-4.

Sample:

Membership of the panel will consist of 2-4 service user representatives (including PAG members) together with health care staff currently involved in IV antibiotic delivery, pharmacists, GPs and other clinicians, NHS commissioners, health economists and a clinical trialist.

Data collection and analysis:

The expert panel will consider which service delivery models and which particular configuration of these models warrant full evaluation in a clinical trial. The panel will consider the design of future clinical trials, identifying ways to overcome potential barriers to service provision and formulate a plan of future research priorities. The panel will also be responsible for devising a strategy to ensure that the dissemination of the research results is optimised.

7 Participant Eligibility

7.1 WP2: Assessment of current OPAT provision by the NHS, establishing reasons for current service configuration and identifying barriers to service provision.

We will conduct a survey of all Acute Trusts in England and use the data collected to identify and recruit OPAT managers/specialists from 30 NHS Acute Trusts. A sampling frame will be constructed using the following characteristics:

NHS Trust Type (Teaching Hospital, Foundation Trust, District General Hospital)

Geographical area (to sample urban/rural and North/South)

Socio-economic status – low and high

Diverse ethnicity.

Types of IV antibiotic services offered.

Some selection criteria will be nested (e.g. hospital type, geographical area) and care will be taken to ensure that all viewpoints representative of UK sites are included.

7.2 WP 3 & 4: Health Economics Cost Effectiveness Study: To assess the relative cost-effectiveness of service models.

We will be collecting data using four different approaches. In each case the population of interest remains the same (see below).

WP 3: Collection of anonymised data.

WP 4: Interviews and Focus Groups (to generate data to construct DCE interviews), 'think aloud/pilot' of DCE items; collection of DCE data via structured interview.

Sample: Purposive sampling via a sampling matrix will recruit participants with different experiences of IV antibiotics services. Sampling characteristics will be:

a) long and short-term treatment patients

b) Patients who have received treatment via one of the following five service designs:

IV treatment as an out-patient (out-patient attendance model)

IV treatment at home by a Community Nurse (visiting general nurse model)

IV treatment at home by a Specialist Nurse (visiting specialist nurse model)

Self-administered IV antibiotics/ treated at home from a family member who has been trained to administer IV antibiotics (e.g. Cystic Fibrosis patients).

IV antibiotics as an in-patient, solely because OPAT (home based) IV antibiotic services are not offered (economic data will not be collected for these patients as these data are available, but they will take part in the DCE.

We will have broad eligibility criteria for patients from the participating NHS Trusts and practices that compromises:

7.3 Inclusion Criteria

Aged 18 years and over

Received IV antibiotics via NHS using any of the models identified above.

Willing to provide data (anonymised or in person) and give informed consent

If a translator is needed, the availability of provision of translation service in the spoken language of the participant via the normal NHS access routes to such services. However, the EQ5D has not been validated in all languages. This may

preclude some participants from taking part in the DCE study (we will assess on a case-by-case basis). These participants would still be able to provide anonymised data and take part in the interview study (with a translator) but not the focus group as this would be a significant burden on the participant, and would affect the focus group discussion.

7.4 Exclusion Criteria

Patients unable to give their informed consent

A sampling matrix for participants will include criteria linked to the objectives of the project including demographic factors (age, gender, ethnicity, socio-economic status), geographic area (urban/rural), IV service category (OPAT/in-patient), antibiotic experience (long or short term IV antibiotics).

8 Recruitment Strategy and Informed Consent

8.1 WP2: Assessment of current OPAT provision by the NHS, establishing reasons for current service configuration and identifying barriers to service provision.

Trust Identification: We will identify NHS Trusts to sample using information from our survey and supplemented by information obtained from public domain literature (e.g. Trust websites). We will send a letter of invitation to NHS Trust Infection Specialists (or OPAT managers where these exist) in all 170 Acute NHS Trusts in England (we are assuming a 30% uptake) with a brief introduction to the study. The letter will formally invite them to participate and will include a Participant Information Sheet and Informed Consent Document (separate ethical approval applied for). This will include information about the rationale, design and implications of the study for the NHS Trust. Staff will be invited to contact the research team at the University of Leeds to find out more information and to discuss the study further. Two weeks later a member of the research team will contact the staff member by phone to ascertain whether they would be willing to take part in a telephone interview. This will provide the opportunity to answer questions and to ask participants to sign two consent forms and return one signed consent form to the Study Project Manager. The signed consent forms will be filed at Leeds Institute of Health Sciences, University of Leeds and this will be used to track recruitment and monitor consent processes.

8.2 WP 3 and 4: Health Economics Cost Effectiveness Study: To assess the relative cost-effectiveness of service models.

Recruitment Strategy for WP 3 & 4: Determination of patient preferences for different community IV antibiotic service attributes through a discrete choice experiment

Patients will be recruited via two routes. Some patients will be identified by NHS clinical staff when in hospital and approached to seek consent. Some patients will be identified retrospectively by a Research Nurse, or clinical co-applicants, through reviews of case notes, and searches of patient records. Eligible patients will be sent a letter of invitation by the NHS Trust and will be provided with written details about the study (Participant Information Sheet and Informed Consent Document) and verbal information. This will include detailed information about the rationale, design and personal implications of the study. Potential participants will be invited to contact the research team at the University of Leeds to find out more information and to discuss the study further. Participants will be invited to take part in WP3 (anonymised data) and asked if they would also be willing to take part in WP4 (DCE)

To achieve a recruitment of 200 patients in WP 3, and 280 patients in WP4 (focus groups, interviews, pilot and main study) recruitment will take place over six NHS Acute Trusts (Bradford, Calderdale,Hull, Leeds, Mid Yorkshire and Sheffield) over a period of 20 months. A total of approximately 100 patients per month are currently treated with IV antibiotics in these areas, and we will also be recruiting patients retrospectively via medical records. In addition, for WP3 alone, as the self- or carer-administration model of care is relatively rare, we will contact centres using this model identified from our Health Professional survey and through the NIHR Infectious Diseases and Microbiology Specialty Group and invite them to participate in the study. This is to ensure we have recruited adequate numbers for the health economics analysis.

At a patient level, inclusion criteria are that patients must be above 18 years of age and must have either a long or short term infection that was treated with IV antibiotics via one of the methods described above. This, together with very broad inclusion criteria and exclusion only on the basis of ability to provide informed consent, leaves us confident that the recruitment period will deliver sufficient patients.

The assessment of eligibility and the informed consent process will be undertaken by authorised members of staff from the NHS Trusts or The University of Leeds who are qualified by training and / or experience in taking informed consent to GCP standards. Informed, written consent for entry into the study must be obtained prior to taking part.

Patients will have as long as they need to consider participating in the study. This will always be more than 24 hours. A member of the research team will discuss the contents of the information sheet with potential participants. Once the research team are confident that participants have understood all of the relevant information, participants will be asked to complete both copies of the consent form and return one to the researcher. Within the information sheet it will be made clear that consent and opting out procedures will be ongoing throughout the process and the voluntary nature of the research will be reinforced at each stage of the research.

We are keen that patients are not over-burdened by their involvement and so we are offering different levels of involvement (shown below in table 1). Due to possible contamination between studies, participants will not be able to take part in the main DCE study if they have already completed the pilot DCE questionnaires. We have created a brief information leaflet for participants so they can consider the opportunities for involvement (see supporting documentation).

Table 1: Table of opportunities for Involvement

Patient Participation level	Option available
WP3: Health economic modelling – providing anonymised data only	Yes
WP3: Health economic modelling providing anonymised data and WP 4 Interviews or focus groups	Yes
WP3: Health economic modelling providing anonymised data and WP 4 Piloting DCE	Yes
WP3: Health economic modelling providing anonymised data and WP4 DCE main data collection *	Yes
WP4: Qualitative focus groups only	Yes
WP 4: Interview only	Yes
WP 4: Pilot Questionnaire only	Yes
WP 4: DCE questionnaire only	Yes

The participant will be given the opportunity to discuss the study with their family and other healthcare professionals before they are asked whether they are willing to take part. This will include information about the purpose of the interviews, the topics to be covered, the DCE study procedure and the anonymised data to be collected, and how confidentiality will be assured. The rights of the participant to refuse consent without providing a reason will be respected; as will their right to withdraw from the study at any time without prejudicing further treatment/care.

Provision of information regarding the studies is permitted by any member of the site research team approved to do so by the Chief Investigator, although the Chief Investigator should be informed of any patients approached to participate by any other member of the site research team.

The original consent forms will be filed in the Investigator Site File, a copy of the consent form will be given to the participant and a copy will be returned to the CIVAS Study Coordinator at Leeds Institute of Health Science, University of Leeds and this will be used to track study recruitment and monitor consent process to GCP guidelines and generate reports to the CLRN and Primary Care Research Network

for service support site payments. A copy of the consent form will be forwarded to the GP practice and held on the patient's record.

Patients who lose capacity will be treated in accordance to the Mental Capacity Act 2005.

8.3 Registration

Registration of participants will be conducted by research staff at each site using a sequential numbering registration system that will provide an individual patient and study site identification number to be used on all study documentation. Participants recruited from GP practices will be registered by study staff at LIHS, participants recruited from acute trusts will be registered by research staff (nurses/clinical) at the study site.

Two levels of information will be required at registration:

For those participants consenting to anonymised data collection only:

Name of person registering patient

Patient's initials

Patient's date of birth

Patient's gender

Patient's first 4 letters of their postcode

Confirmation of eligibility

Date of written informed consent

For those participants consenting to attend the focus groups/interviews/DCE

Patient's address and their postcode

Patient's telephone number

Indication if translator service required and what language spoken

General demographic information: marital status, employment status, education, ethnicity/nationality, details of IV infection experiences.

8.4 Non-registration

Each Trust will be required to complete a log of all patients screened for eligibility who are not registered either because they are ineligible or because they decline participation. Anonymised information will be collected including:

age

gender

ethnicity

date screened

education

marital status

reason not eligible for participation in the study OR

eligible but declined and reason for this OR

other reason for non registration

This information will be collected on an approximately 3 monthly basis by the Leeds Institute of Health Sciences.

8.5 Withdrawal

Where participants wish to withdraw from the study the type of withdrawal will be clarified (withdrawal from whole study or sub-study) and subsequent recording of these data to ensure participants are not approached again.

9 Intervention details

This is not an intervention study. It is a cross-sectional observational study of 400 patients to explore their views of patient preferences for different methods of IV antibiotic delivery.

10 Data collection

10.1 WP2: Qualitative data collection.

A range of OPAT staff will be identified and approached for consent to provide a purposeful sampled group of NHS OPAT managers/infection control consultants. Data will be collected via structured survey and semi-structured interviews.

10.2 WP 3 & 4: Quantitative Data Collection:

A data collection form (see supporting documentation) has been developed to collect the following anonymised data:

socio-demographics

treatments received and their effectiveness

Adverse outcomes and side-effects

their location and duration of treatment

treatment delivery systems

additional health services used

In addition, participants taking part in the DCE will provide DCE responses and the following additional data: EQ-5D, treatment satisfaction and attitudes towards OPAT treatments and the NHS.

10.3 WP4: Qualitative data collection

WP3: A range of patients will be identified and approached for consent to provide a purposeful sampled group of patients to take part in focus groups (n=40). In addition, 10 IV antibiotic patients (5 long term and 5 short term) will be identified through theoretical sampling to be interviewed.

WP4: Thirty patients will be identified to take part in a pilot study of the DCE survey

Data will be collected via semi-structured interviews and focus groups using standard methodology. Data collection will be informed by a topic guide (draft enclosed). All data will be recorded, transcribed verbatim and analysed using thematic content analysis. In addition, demographic information will be collected using the tool devised for WP3 (appendix 5).

11 Avoidance of Harm

11.1 Harm to Participants

It is not envisaged that participants will experience any adverse implications as a result of taking part. However, the project's information sheet will detail the potential risks involved in taking part. For example, participating in the study may evoke some negative thoughts or emotions regarding the care and treatment they received for their infection(s).

In order to minimise the possibility of participants experiencing negative consequences they will be advised in the information sheet that they do not have to answer any questions they do not wish to and are free to withdraw from the study at any time.

11.2 Potential Harm to Researchers

In the event that participants need additional support/information during the study it is possible that a member of the research team may need to meet the participant. All meetings with participants will take place ideally within normal working hours (Monday to Friday 9am to 5pm) at a mutually convenient location. Some focus groups and qualitative interviews may take place in the evening. We are planning to conduct the DCE interviews in participants' own homes and the University of Leeds Lone Working Policy will be put in place to ensure safety (researcher would be accompanied by an assistant or would have to telephone an assistant to let them know whereabouts post interview).

Before the meetings a 'safe' location for both the researcher and participant will be agreed upon. If the participant requests that the meeting takes place at their home then the interview setting will be discussed with the PI and a risk assessment will be carried out by the PI before the meeting. The Principal Investigator (PI) and Project Manager will be informed of the venue, date and time of all interviews and the researcher will inform the PI when they arrive, and safely depart from their meeting with the participant by telephone.

12 Endpoints

This is not an outcomes study so there are no endpoints of interest.

13 Data Monitoring

Data will be monitored for quality and completeness by the Project Manager. Missing data will be chased until it is received, confirmed as not available or the study is at analysis. The Chief Investigator and their nominated persons/Sponsor

will reserve the right to intermittently conduct source data verification exercises on a sample of patients, which will be carried out by staff from the Chief Investigator/Sponsor. Source data verification will involve direct access to patient healthcare records and the collection of copies of consent forms and other relevant investigation reports. A Study Monitoring Plan will be developed.

14 Clinical Governance Issues

To ensure responsibility and accountability for the overall quality of care received by patients during the study period, clinical governance issues pertaining to all aspects of routine management will be brought to the attention of the Study Steering Committee/Advisory Board and, where applicable, to the participating NHS Trust.

15 Quality Assurance and Ethical Considerations

15.1 Quality Assurance

The study will be conducted in accordance with the principles of Good Clinical Practice, the NHS Research Governance Framework and through adherence to University of Leeds Standard Operating Procedures (SOPs) as appropriate.

15.2 Ethical Considerations

The study will be performed in accordance with the recommendations guiding physicians in biomedical research involving human subjects adopted by the 18th World Medical Assembly, Helsinki, Finland, 1964, amended at the 48th World Medical Association General Assembly, Somerset West, Republic of South Africa, October 1996. Informed written consent will be obtained from the patients prior to registration into the study. The right of a patient to refuse participation without giving reasons must be respected. The patient must remain free to withdraw at any time from the study without giving reasons and without prejudicing his/her further treatment. The study has been submitted to and approved by XXXXXXX NRES Committee.

15.3 Confidentiality

All information collected during the course of the study will be kept strictly confidential. Information will be held securely on paper, electronically and digitally (for the recordings of the Qualitative interviews) at the Leeds Institute of Health Science, University of Leeds who will comply with all aspects of the 1998 Data Protection Act and operationally this will include:

Consent from patients to record personal details including name, date of birth,

Appropriate storage, restricted access and disposal arrangements for patient personal and clinical details.

Consent from patients for access to their healthcare records by responsible individuals from the research staff or from regulatory authorities, where it is relevant to study participation.

Consent from patients for the data collected for the study to be used to develop new research.

Patient name will be collected when a patient is registered into the study but all other data collection forms that are transferred to or from the research sites will be coded with a study number and will include two patient identifiers, usually the patient's initials and date of birth.

Where anonymisation of documentation is required, sites are responsible for ensuring only the instructed identifiers are present before sending to University of Leeds.

If a patient withdraws consent from further intervention and / or further collection of data, all collected data will always be included in the final study analysis.

15.4 Archiving

At the end of the study, data will be securely archived in line with the Sponsor's procedures for 15 years. Data held by the research teams, will be locally archived or as instructed by sponsor where it is typically stored in the Leeds Sponsor archive facility and site data and documents. Following authorisation from the Sponsor, arrangements for confidential destruction will then be made.

16 Statement of Indemnity

16.1 Research Governance

The Leeds Teaching Hospitals NHS Trust, which is the host institution of Dr Minton will sponsor the study. The study will be conducted in accordance with the principles of Good Clinical Practice, and the Department of Health Research Governance Framework for Health and Social Care, 2005. The study will not be initiated before it has obtained necessary approvals from the respective IRAS and National Health Service (NHS) Research & Development (R&D) departments.

As this is a clinician-led study there are no arrangements for no-fault compensation.

17 Project Management

17.1 Responsibilities

Chief Investigator - The Chief Investigator, as defined by the NHS Research Governance Framework, is responsible for the design, management and reporting of the study. They will have responsibility for conduct of the study in accordance with the Research Governance Framework and Universities of Leeds Standard Operating Procedures (SOPs) as appropriate.

17.2 Study monitoring

Study supervision will be established in line with MRC GCP guidelines and will include a core team who will form a Study Management Group (SMG). The SMG will be responsible for implementation and will meet monthly during set-up and at least quarterly throughout the study. The SMG, comprising the CI, and co-investigators will be assigned responsibility for the set-up, on-going management, promotion of the study, and for the interpretation of results. Specifically the SMG will be responsible for (i) protocol completion, (ii) CRF development, (iii) obtaining approval from the main REC and supporting application for Site Specific Assessment, (iv) completing cost estimates and project initiation, (v) reporting of related unexpected serious adverse events, (vi) monitoring of screening, recruitment, treatment and follow-up procedures, (vii) auditing consent procedures, data collection, and database development. They will be supported by an appointed Research Assistant and Research Fellow and the local Infection research nurse team.

17.3 Project Manager

Dr Maureen Twiddy (Co-applicant) will work with Dr Minton to provide day to day project management of the study including study administration, data management, and safety reporting under the direction of the CI. Specifically, MT will co-ordinate the set-up and monitoring of the study according to Leeds Institute of Health Sciences standard operating procedures (SOPs) including protocol development. She will work to support the main REC, Site Specific assessment and R & D submissions, and on-going monitoring and promotion of the project.

Together with the CI the project manager will have responsibility for supporting the Patient Advisory Group and the PPI co-applicant, including sourcing relevant training courses. The PI and PM will have joint responsibility for supervision of research nurses/assistant/ fellow. MT and JM will meet fortnightly with the researchers to monitor progress of the study and maintain timeline and delivery to target.

17.4 Study Management Group

A Study Management Group (SMG) will direct and oversee the running of the study. The SMG, comprising the CI and all co-investigators will be assigned responsibility for the set-up, on-going management, and promotion of the study and for the interpretation of the results. Specifically, the SMG will be responsible for a) protocol completion; b) monitoring of recruitment and data collection; c) auditing consent procedures; d) database development. They will be supported by the project manager (a co-I) and an appointed research assistant. The team will meet quarterly.

17.5 Core Project Team

In addition to the SMG meetings, the leads for each work stream will meet with the CI monthly to monitor progress and ensure timely delivery of study.

HS & DR Project Core Project Team					
Chief Investigator	Project Manager	1: Systematic Review	2: Evaluation of current service provision	3: Economic modelling & CEA	4: Discrete choice experiment
Jane Minton (Mentor: Claire Hulme)	Maureen Twiddy (supported by Sandra Holliday : Finance)	Carolyn Czoski Murray	Carolyn Czoski Murray	David Meads Claire Hulme	Stephan Hess David Meads M Twiddy

17.6 Study Steering Committee

A Study Steering Committee (SSC) will be constituted to oversee advice on and monitor the study progress. The SSC will play a significant role in supporting the Study Management Group to deliver the study and providing strategic advice.

The SSC will meet annually or as they deem necessary. We will follow the sponsor's proposed time period for retention of relevant anonymised clinical data of 15 years following the end of a study (according to the MRC guidelines). The University of Leeds will archive all paper and electronic records in a legacy format according to GCP requirements.

17.7 Public Involvement

The PAG will be involved throughout the project, and have had input into this ethical review application as well as the original grant application. The PAG group will meet regularly during the lifetime of the study to provide input into the ongoing management of the study. The group have already provided practical input into the design of the data collection tools, information sheets and consent forms. During the study they will be asked to comment on the literature review protocol, topic guides and results, and to help interpret the economic modelling and DCE results.

They will also be invited to the expert panel to contribute to discussions regarding optimal service delivery.

One member of the PAG is a co-applicant and is a full member of the research team and is invited to monthly research team meetings. The PPI Co-applicant is also a member of the study steering committee (a second PAG member will be invited to join this committee).

A team member with considerable experience of PPI (Dr Maureen Twiddy) will support the PAG and provide research mentorship to facilitate meaningful involvement in the project. PAG members will be reimbursed for their time and travelling expenses will be paid. Training will be offered to PAG members to build up their skills and knowledge of research.

18 Funding

This study is funded by the National Institute for Health Research (NIHR) Health Services Research and Development funding stream (HS & DR) (Ref: 11/2003/60)

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