

Research Protocol Protocol

Longitudinal Evaluation of Patient Outcomes and Impact Assessment on Family Members of Home Parenteral Nutrition: New Directions for Research

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Introduction

Providing a person with food through a vein is known as parenteral nutrition (PN) or artificial tube feeding. This process is used when nutrients from food can't be taken in by the intestine (intestinal failure). Patients with type 3 intestinal failure are completely reliant on artificial feeding and often manage this at home; home parenteral nutrition (HPN). HPN therapy is life saving for these patients.

It is important to assess patients quality of life and their own reported effects of the HPN. The Parenteral Nutrition Impact Questionnaire (PNIQ) is a proven tool for measuring quality of life when receiving HPN.

A recent study involving the use of the PNIQ in multiple hospitals in the UK, showed that those on fewer nights of HPN had better quality of life than those on more nights of HPN. Whilst this was useful for looking at quality of life at one time point, it is now important to assess change in quality life over time and any impact on family members quality of life.

This study will recruit HPN patients across the UK and ask them to complete the PNIQ survey at several different time points. This will assess the impact of HPN over time. Family members involved in the participants HPN care will also be asked to complete a carer burden survey (at one time point) to assess the impact of HPN on carers.

The study is being funded by Shire Pharmaceuticals Ltd.

Background

Quality of life in people with intestinal failure

Patients with Type 3 intestinal failure (IF) are dependent on parenteral support which may include fluids, electrolytes or nutrients [1]. From a recent national survey in the U.K., the point prevalence of patients dependent on home parenteral nutrition (HPN) was 1144 and 34% of these patients had a diagnosis of short bowel syndrome (SBS) [2]. Although HPN is recognised as a lifesaving therapy for these patients, it is not without risks. The complications of parenteral nutrition (PN) are serious and include catheter related blood stream infections leading to septicaemia, and the presence of a central venous catheter can cause thrombosis and embolism [3]. There are also more long-term adverse complications including hepatic failure and osteoporosis [4].

It is also well documented that patients who require HPN have a decreased quality of life (QoL) [5; 6]. Moreover, it has been established that people dependent on PN have higher rates of depression compared to the general population, suffer a higher rate of anxiety and are unlikely to ever return to meaningful employment [5; 7]. Other factors that affect QoL include use of opioids, nocturia, the presence of a stoma, age and the number of infusions required per week [8; 9; 10].

The ability to be able to assess patient reported outcomes for different treatments is now essential for patients with chronic IF; the Parenteral Nutrition Impact Questionnaire (PNIQ) provides a validated tool to evaluate differences in needs based QoL.

From a recent large multi-centre U.K. survey, we have now established face validity of the PNIQ and also reported a clinically meaningful difference between patients with different underlying diseases as well as between patients requiring different numbers of nights of PN. The survey demonstrated PNIQ was sensitive to change in treatment delivery and there was an increase in PNIQ score (reflecting improved QoL) in those individuals dependent on fewer nights of HPN [11]. While this survey assessed QoL at one time point, face validity addressing within person variation over time is now required. It is important for clinicians and patients to evaluate the impact of changes in HPN burden over time, as well as any impact of changes in treatment modalities. New technologies within intestinal failure, including the introduction of growth factors to patients with SBS, have led to the increased demand for tools with comprehensive validity assessments to be able to measure patient reported outcomes.

The ability to be able to assess patient reported outcomes overtime in a large cohort of patients with IF-SBS is therefore very timely with new innovations imminent within the UK landscape. The assessment tool used will be able to show any changes that occur over time in relation to modifications in HPN provision. Treatment changes may be due to gastrointestinal adaption, small bowel transplant or use of new growth factors.

Family member's research

In contrast to patients on HPN there is a paucity of research on QoL experienced by family members of people dependent on long-term HPN. The impact on family members of people needing HPN with advanced cancer has been evaluated and family members reported feeling very responsible for their relative [12]. A survey of 178 families, with a family member with advanced cancer dependent on HPN, demonstrated that family members provided daily

support for patients on HPN but were faced with challenges including loss of friends, loss of employment and depression [13]. However, while these studies describe the impact of HPN burden on the family of patients with advanced cancer and palliative needs, there are no comparable data detailing the impact of living with a family member on HPN with a chronic, long term, benign underlying condition. Prior to investigating methods of providing support for family members of people on HPN it is essential to investigate the experiences of family members and carers. Once this has been determined then the necessity to intervene to provide support can be evaluated.

New innovation in treatments

Recently, the development of growth factors, such as glucagon-like peptide 2 analog (Teduglutide), aimed at enhancing small bowel absorption, has changed the landscape of therapeutic options available for people with SBS [14]. Teduglutide (Revestive® Shire Pharmaceuticals) enhances fluid, electrolyte, and nutrient absorption. It is indicated in the treatment and management of SBS-associated IF (SBS-IF). Teduglutide is an analogue of glucagon like peptide 2, a naturally-occurring hormone which promotes the growth of nutrient absorbing cells on the surface of the intestine.

Teduglutide reduces HPN requirements by enhancing absorption requirements; hence, PNIQ is an ideal measurement tool to assess this and other treatment modalities. The ability to assess outcomes in patients on HPN and their family members is required so new innovations in treatments and service provision can be fully evaluated. The introduction of new technological innovations in the UK is imminent so this research is timely as it will assess patient reported outcomes prospectively allowing for any changes to be reported pre and post the introduction of innovations within the UK population

Future direction of research that is required for patients and their families can be explored by implementing a James Lind Priority Setting Partnership between healthcare professionals, patients and family members.

The intestinal Failure Unit (IFU) at Salford Royal Foundation Trust (SRFT) currently manages around 280 patients on long-term PN throughout the UK. Each year there are 63 new patients discharged from the Unit at Salford whilst on PN.

The proposed project is therefore a logical development in assessing the validity of PNIQ by addressing changes over time in a national cohort of HPN patients. It is also necessary to

determine the impact on families of long-term HPN. However, to develop research for people receiving HPN, this proposal also incorporates a Patient and Professionals Priority Setting Partnership to be registered with the James Lind Alliance. This is a process whereby research priorities are set independently with health care professionals and patients.

Study objectives

1. Systematic review of the literature of quality of life in patients and their families on HPN with intestinal failure.
2. To determine patient reported outcomes using PNIQ longitudinally in people receiving HPN.
3. Assess the impact of living with a family member dependent on HPN.

Study design and protocol

Study 1: Systematic Review

Undertake a systematic review of research on QoL in patients receiving HPN with full quality assessment.

Study 2: Longitudinal assessment of quality of life in people receiving HPN

Objective: To measure patient reported outcomes longitudinally in people receiving HPN.

Patient reported outcome: The Parenteral Nutrition Impact Questionnaire (PNIQ)[®] was developed from undertaking semi-structured qualitative interviews with people on HPN to identify ways in which need fulfilment was impaired by HPN. The interviews were used to develop a questionnaire for a postal survey undertaken in two NHS Trusts. The survey had the purpose of developing items for scale, scaling properties including unidimensional properties, construct validity and reproducibility. The survey was sent out twice to a proportion of respondents to determine intra-rater reliability. Cognitive debriefing interviews were then performed to check the relevance of the scale, clarity and ease of use [15]. This enabled ratification of themes relevant to people living with HPN. The tool was also validated against the Nottingham Health Profile [16].

There is currently a paucity of longitudinal data for patients on HPN using any tool. This proposed study now looks at determining longitudinal face validity and aims to determine if PNIQ score is sensitive to length of treatment and treatment changes, if any, over time. The

frequency of administration of PN, and other changes in QoL including Short version 36 questionnaire (SF-36) and EQ-5D

Method: Design of the proposed study is a longitudinal observational cohort study and data will be collected using a questionnaire sent to participants as a national postal survey. Patients may also receive the questionnaire via a clinic appointment or via email. The PNIQ will be used along with a brief questionnaire to collect participant's characteristics and demographics. Questions will also be included on recent changes in treatment, length of time on PN, frequency of PN infusions per week, re-admissions to hospital and any changes in medications. We will also include EQ-5D-5L generic health questionnaire and a questionnaire that measures Activities of Daily Living Questionnaire, to assess generic QoL.

PNIQ Tool: The PNIQ is made up of 20 questions. The questions are specifically related to HPN and aim to assess QoL and the overall impact of treatment in those who receive HPN. Each statement on PNIQ has a dichotomous response 'True' or 'Not true'. Each response is allocated a score of 1 for 'True' and a score of 0 for 'Not true'. All item scores are summed up to give a total score ranging from 0 (good quality of life) to 20 (very poor quality of life).

Study 3: Assessing the impact of HPN on families and partners.

This study will be run in conjunction with the patient survey above to assess family members' quality of life.

Objectives: Assess the impact of living with a family member on HPN. Explore family members' and caregivers' experiences of living with a patient with IF on HPN.

Recruitment: We will aim to recruit 300 hundred family members or caregivers of patients who are having HPN. We will ask each patient recruited for Study 2 to nominate a family member to this survey. The family members'/care givers' survey will be sent to the patient along with the survey that they are to complete themselves. Both surveys can be returned in the freepost envelope that will be provided. A receipt of a completed family member survey will be taken as consent.

Timelines

Timelines for longitudinal survey and study of family members' experiences.

	Year 1			Year 2			Year 3		
Systematic Review: Study 1									
Undertake and complete review									
Longitudinal QoL: Study 2									
Study set up									
Patient recruitment									
Follow up									
Data inputting									
Data Analysis									
Write up for longitudinal study									
Family members: Study 3									
Study set up									
Participant recruitment/survey									
Data inputting									
Data Analysis									
Write up for family members/care givers survey									

Study participants

Study 2: Longitudinal assessment of quality of life in people receiving HPN

Recruitment: Each hospital will who agrees to take part will recruit participants from National Health Service (NHS) locations throughout England. The direct clinical care team at each NHS location will identify and recruit patients with type 3 intestinal failure requiring HPN.

Inclusion criteria: All people in receipt of HPN due to type 3 intestinal failure including new patients and those 18 years and over.

Exclusion criteria: Those who cannot give informed consent and cannot read or write in English.

Upon identification, participants will be sent a pack which includes all explanatory study documentation and questionnaires. Completion and return of the questionnaires will be taken as consent. As this is a longitudinal survey we will ask participants if they are happy to be contacted directly by the research team and disclose their names and addresses (consent to contact), thus enabling the researchers to send out (post or email) follow up questionnaires at 5 monthly intervals. The first of the follow up questionnaires will be sent along with a participant information sheet and the participant will be asked to complete and return written consent in order to formally consented onto the study. Data from follow up surveys will only be entered into the study if written consent is provided.

Sample size: Given the study design, a formal comparison test suitable for a sample size calculation is not available for the main survey proposed. Hospitals with substantial HPN populations will be identified and considered as potential sites for this study. At least 15 sites will be identified with an overall estimated total of 1400 patients receiving HPN. A previous survey in patients with HPN, conducted at Salford Royal Foundation Trust had a response rate of 45% across two study sites, indicating an expected sample size of 630 could be achieved if all 1400 patients were approached for this study.

Given the number of subjects approached in the previous study (n=506) an 80% binomial confidence interval (CI) of 43% to 49% for the 45% response rate indicated that we had an 80% confidence in a response between 447 and 510, or 90% confidence of a sample size greater than 447.

Study 3: Assessing the impact of HPN on families and partners.

Recruitment: Family members will be nominated by eligible patient participants, who will receive both the patient survey and family member survey.

Inclusion criteria: A family member or person involved in the healthcare of the participating patient. We will ask patients to nominate their closest family member or friend who in their opinion is potentially most effected by the parenteral feeding.

Exclusion criteria: Family members not directly involved with caring for participants.

The study pack sent to patients will also contain the family member survey and extra study information will be provided within this survey for the family member to read. Completion and return of the survey will be taken as family member consent. No personal or contact details will be asked for in the family survey.

Sample size:

Based on the sample size from the patient survey and assuming that we receive 50% response rate from family members we expect a sample size of 300.

Outcome measures

For the patient survey the primary outcome will be patient reported PNIQ score. Other outcomes of interest will include the participants' age, gender, disease state and socio-economic group. Secondary outcome measures relating to PN will include; frequency and duration of time on PN; treatment changes; medication alterations, diagnosis and changes in social circumstances.

For the Family member survey the primary outcome will be carer burden score and quality of life. Other outcomes of interest will include: Employment status, educational attainment, income category, recent medication or hospital care received, and how supported they feel in the carer role.

Data Collection, Source data and Confidentiality

The initial patient survey sent out by the clinical team will be allocated an identification number, which will be noted by each centre and a recruitment log will be completed. This will allow for linkage back to the participant without sharing identifiable participant details

with research team members (pseudonymisation). If a participant provides their contact details on the first survey these details will be received by the research team. Upon receipt of personal details the research team will immediately separate these from the survey data and replace with the participants ID number. Personal details and survey details will be entered into separate electronic database and a secure pseudonymisation key will be created. All databases will be stored within the University of Manchester's Research Data Storage (RDS) system. During the course of this study, if we have any concerns about the safety or safety of others we will need to break confidentiality and inform the patients hospital care team. We will adhere to the guidelines specified by General Data Protection Regulations (GDPR 2018).

The family member survey will be sent out by the clinical team and will be allocated an identification number, which will be noted by each centre and a recruitment log will be completed. This will allow for linkage back to the participant without sharing identifiable participant details with research team members (pseudonymisation). The family member survey will not ask for consent to contact and so no identifiable information will be received by the research team.

Statistical considerations

The responses from patient study participants will be summarised and reported using standard descriptive statistics and appropriate graphical techniques. Factors influencing the primary outcome, of the PROMs PNIQ score, will be investigated in the form of an exploratory analysis. Factors of interest include the participants' age, gender, disease state and socio-economic group. Secondary outcome measures relating to PN, including; frequency and duration of time on PN; treatment changes; medication alterations, diagnosis and changes in social circumstances will be investigated. In each case the appropriate regression model will be chosen given the structure of the outcome of interest (continuous, binary, ordinal). The factors of interest will be investigated, initially individually in an unadjusted model and then adjusted for potential confounders chosen a priori. Where possible, given the information recorded, measures will be taken to account for potential bias due to clustering of subjects within NHS sites, non-response characteristics, and sample specific characteristics. All appropriate goodness of fit and model assumptions will be checked and measures will be taken into account for any departures. The presence

of multiple testing will be monitored and steps will be taken to adjust the p-value accordingly.

The responses from family member study participants will be summarised and reported using standard descriptive statistics and appropriate graphical techniques. Difference between groups will be explored including disease states, age, gender, and frequency of HPN infusions per week whilst at home, length of function bowel, length of time on HPN, disease classification.

Data monitoring and quality assurance

The study will be subject to the audit and monitoring regime of the University of Manchester. Quarterly reports will be provided to the funder (Shire International) via an electronic portal.

Safety considerations and adverse events

As this study is survey based there will be no risks or adverse events.

Peer review

Clare Donnellan from Leeds Teaching Hospitals NHS Foundation Trust and Martyn Dibb from Royal Liverpool University Hospital have both reviewed and provided a letter of support.

In addition, the nutrition research team at the University of Manchester have reviewed and approved the scientific quality of the research.

Ethical Considerations

Approvals

All governance and ethical approvals will be obtained prior to starting the project.

NHS Research Ethics Committee approval will be obtained before commencing research. The study will be conducted in full conformance with all relevant legal requirements and the principles of the Declaration of Helsinki, Good Clinical Practice (GCP) and the UK Policy Framework for Health and Social Care Research 2017.

Risks

There are no risks associated with completing a survey. The survey is not of a sensitive nature. However, all surveys will be monitored by the research team and any sensitive issues that arise will be passed onto the clinical team

Statement of indemnity

The University has insurance available in respect of research involving human subjects that provides cover for legal liabilities arising from its actions or those of its staff or supervised students. The University also has insurance available that provides compensation for non-negligent harm to research subjects occasioned in circumstances that are under the control of the University.

Funding

This project is funded by an unrestricted research grant from Shire International GmbH.

Publication policy

Following completion of the study the results will be published in open access, peer reviewed journals.

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