Study Protocol

Full Title:

The Role of Different Diets in Children who are Gastrostomy Fed; a mixed methods exploratory sequential study

Short title:

The Role of Different Diets in Children who are Gastrostomy Fed

Version and Date of Protocol:

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Protocol Version Number and Amendment History

Version	**Author**	**Date**		
1.0	Lorna Fraser	09/01/2019		
Amendments				
Version	**Author**	**Date**	**Changes made**	**Approved**
1.1	Jo Taylor	05/03/2019	Amended recruitment and consent process to address issues raised by ethics review Added Appendix A	**25/03/2019**
1.2	Jo Taylor	02/12/2019	Added face-to-face contact with families who require assistance with completing data collection questionnaires. Added destroying of records for families who return consent-to-contact forms but don't provide consent to participate. Added collection of demographic and feeding information pre-baseline. Removed the word "personal" in the paragraph which describes who can be a consultee.	**20/12/2019**
1.3	Jo Taylor	13/08/2020	Updated processes for recruitment, consent and data collection for WS2, which were implemented due to Covid-19. Added Appendix B which provides updated WS2 inclusion criteria (informed by WS1 findings and decided by the Study Steering Committee (SSC)). Added Appendix C which provides a summary of the agreed outcomes and variables to be measured in WS2 and the decision about how formula and blended groups will be categorised (informed by WS1 findings and decided by the SSC).	**28/08/2020**
1.4	Jo Taylor	20/04/2021	Incorporated the following study amendments as recommended by	

			the Study Steering Committee to help ensure the study delivers on its objectives following the impact of Covid-19: • Change the 9 month follow-up to a 12 month follow-up • Request HES data for baseline and 12 month follow-up only (not for the 18 month follow-up) We have also implemented the following changes to the data collection processes to minimise burden on participating families and maximise potential to obtain baseline data from families: • Removed collection of demographic and feeding data pre-baseline and incorporated into baseline assessment • Reduced number of food diary days from 4 to 3, and allowed for non-consecutive days where parents need this flexibility • Request baseline data from families following consent rather than waiting for next routine appointment For clarity to readers (e.g. local site investigators) we have made clear that the Gantt chart included in the protocol was the original timetable to be revised in line with study progress.	

Contents

1. Study Summary Information

Study Title	The Role of Different Diets in Children who are Gastrostomy Fed; a mixed methods exploratory sequential study
Study Design	Two stage mixed methods study: qualitative and prospective cohort study
Study Participants	Health professionals (paediatricians, SALT, Dieticians, community nurses) Children who are gastrostomy fed and their parents
Planned Size of Sample	664
Follow up duration (if applicable)	18 months for the cohort study
Planned Study Period	Feb 2019-July 2022
Research Question/Aim(s)	What are the risks, benefits and resource implications for using home-blended food for children with gastrostomy tubes compared to currently recommended formula feeds?

2. Key Roles and Responsibilities

SPONSOR: The sponsor is responsible for ensuring before a study begins that arrangements are in place for the research team to access resources and support to deliver the research as proposed and allocate responsibilities for the management, monitoring and reporting of the research. The Sponsor also has to be satisfied there is agreement on appropriate arrangements to record, report and review significant developments as the research proceeds, and approve any modifications to the design.

FUNDER: The funder is the entity that will provide the funds (financial support) for the conduction of the study. Funders are expected to provide assistance to any enquiry, audit or investigation related to the funded work.

CHIEF INVESTIGATOR (CI): The person who takes overall responsibility for the design, conduct and reporting of a study. If the study involves researchers at more than one site, the CI takes on the primary responsibility whether or not he/she is an investigator at any particular site.

The CI role is to complete and to ensure that all relevant regulatory approvals are in place before the study begins, ensure arrangements are in place for good study conduct, robust monitoring and reporting, including prompt reporting of incidents. This includes putting in place adequate training for study staff to conduct the study as per the protocol and relevant standards.

The Chief Investigator is responsible for submission of annual reports as required. The Chief Investigator will notify the REC of the end of the study, including the reasons for the premature termination. Within one year after the end of study, the Chief Investigator will submit a final report with the results, including any publications/abstracts to the REC.

CO-INVESTIGATOR (Co-I): The persons who together with the CI form the management team for the study and provide the necessary expertise required to conduct the study.

PRINCIPAL INVESTIGATOR (PI): Individually or as leader of the researchers at a site; ensuring that the study is conducted as per the approved study protocol, and report/notify the relevant parties – this includes the CI of any breaches or incidents related to the study.

3. Study Personnel

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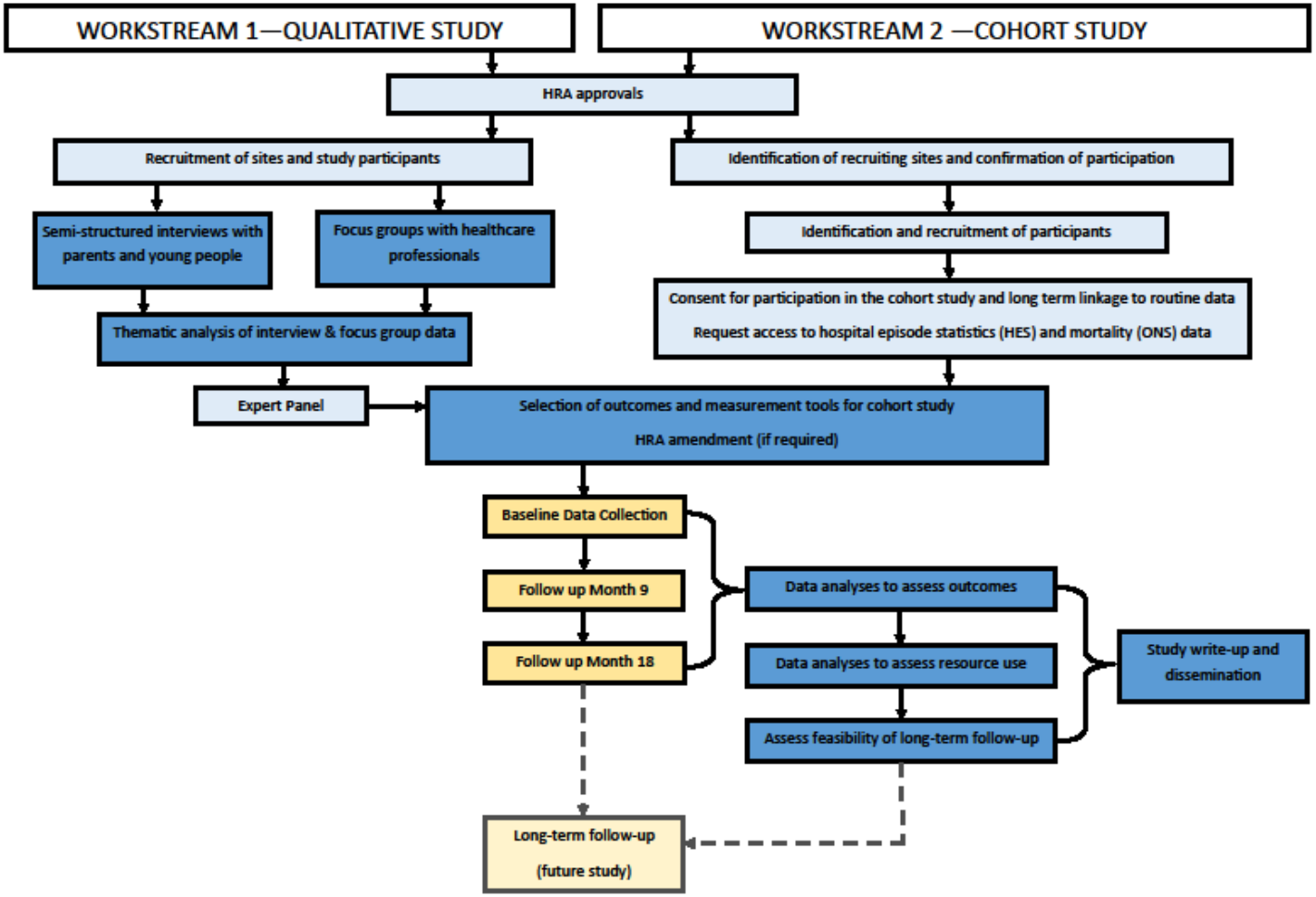
4. Study Flow Chart



5. Summary

Background

There are increasing numbers of children with complex health care needs that require having all, or part, of their nutritional intake via gastrostomy feeds. The recommended feed for children via gastrostomy is commercially produced formula (1). However there is a growing body of parents who are interested in and/or choosing to feed their children home-blended meals (2, 3). These parents often report benefits such as improved gastro-oesphageal reflux symptoms, less constipation and less distress in their child (4). The need for further research in this area has come from a research prioritisation exercise (5), recent review of the literature (6) and professional organisations e.g., British Dietetic Association (1).

Aims

The overall research question for this two stage study is:

What are the risks, benefits and resource implications for using home-blended food for children with gastrostomy tubes compared to currently recommended formula feeds?

Objectives:

1. To identify the important outcomes of gastrostomy feeding for parents, young people and health professionals.
2. To assess the safety of home-blended diets for children who are gastrostomy fed compared to liquid formula diets.
3. To identify and quantify the benefits of home-blended diets compared to liquid formula diets for children who are gastrostomy fed and their parents.
4. To identify and quantify the resources (family and statutory services) required to support home-blended diets compared to liquid formula diets.
5. To assess whether long-term follow-up of children who are gastrostomy fed is feasible using routine data sources.

Research Plan

Work stream 1 (objectives 1-4): a qualitative study involving young people, parents and health professionals will provide foundational evidence with regard to the design of Workstream 2 in terms of choice of outcome measures, other data to be collected, and the feasibility and acceptability of proposed data collection methods. It will gather data on desired outcomes of gastrostomy feeding, variability in diets and reasons for variation; oral feeding, reasons for, and perceived contribution to child's nutrition)(7); the perceived benefits of the alternative diets, and patient safety issues experienced due to gastrostomy feeding and/or the diet used. Findings from WS1 will be reviewed at a meeting with the Study Steering Committee at which final decisions will be made about outcome domains and measures to be used, other data collection requirements, and minimising respondent burden.

Work stream 2 (objectives 1-5): a cohort study of 300 children (1:2 home-blended to formula) who are gastrostomy fed and a mechanism to assess the feasibility of long term follow up using routine data.

These children and parents will be recruited via general, community and specialist paediatric services and children's nutrition and dietetic services. Data will be collected at months 0, 12 and 18 from parents, children (if appropriate) and clinicians using standardised measures and questionnaires developed specifically for the study. Data collected will include gastrointestinal symptoms, quality of life of child and parent, dietary intake, anthropometry, healthcare usage, safety outcomes and resource use.

Benefit and Impact

The beneficiaries of this research will include children with complex health conditions, their families and health care professionals through providing high quality evidence on the risks and benefits of using blended diets.

6. Background and rationale

There are growing numbers of children with complex health conditions that are dependent upon medical technologies to maintain their health, and gastrostomy (or enteral) feeding is one such technology. The applicants' own analyses of inpatient hospital (Hospital Episodes Statistics(HES)) data (conducted in preparation for this bid) found that, for children with life-limiting conditions (LLC) in England, the number having permanent gastrostomy surgery each year has risen from 183 in 2000/01 to 1004 in 2014/15. The total number of children, with a LLC, aged 0-19 in England who have ever had a gastrostomy in 2014/15 was 10,154. This is much higher than the estimates in the published literature of ~430 children (8).

Children requiring some or all of their nutrition via gastrostomy tubes have a wide range of underlying diagnoses including neurodisability, inherited metabolic diseases, congenital cardiac conditions, cystic fibrosis, gastrointestinal diseases and cancer. There are little data available on which families are choosing to use a home-blended diet for their children but we suspect that concerns over the risk of infection and closely monitored fluid intake would mean that this is not an option for some of these children (e.g. those with cancer or cardiac disease).

At present, in the UK, the recommended feed for children on enteral feeding is commercially produced complete liquid nutrition (formula), prescribed by the child's dietitian (1). However there is a growing body of parents who are interested in and/or choosing to feed their children meals they have prepared themselves which are then liquidised so they can be administered via a gastrostomy (referred to forthwith as 'home-blended foods') (2, 3). Parents choosing to use home-blended foods often report benefits such as improved gastro-oesphageal reflux symptoms, less constipation and less distress in their child (4). There are also perceived psychosocial benefits in that the child is being nurtured by the parent and is able to share the same food as the rest of the family and take part in family meal times. Prescribed formula, in contrast, is seen as a medical product rather than food.

Limited research evidence (9) and reports from clinicians suggest that the long-term use of gastrostomy feeds for children with complex health conditions can result in complications including progressive feed intolerance/ gut failure. There are limited options to manage gut failure in this population of children and young people, with the median survival after the onset of such symptoms estimated to be around 50 days (9). There are suggestions that a home-blended diet may reduce the risk of gut failure but there is currently no evidence to support this.

Recent national surveys of paediatric dietitians in the UK (2) and the US (3) both found that more than half of respondents would recommend the use of a home-blended diet (56 and 58% respectively). In the UK, however, that recommendation was to use home-blended food as a supplement to formula feeds rather than their exclusive use. In both surveys the need for further evidence was highlighted.

At the same time, concerns have been raised by professional organisations, including the European Society for Paediatric Gastroenterology Hepatology and Nutrition (ESPGHAN) and British Dietetic Association (BDA), about the risks associated with a diet of home-blended foods. These include: nutritional inadequacy, microbial contamination and blockage of the gastrostomy tube. There are policy/position statements from such organisations stating that they do not recommend that children (or adults) are fed home-blended foods through their gastrostomy tubes. This includes the recently updated ESPGHAN guidelines for the Evaluation and Treatment of Gastrointestinal and Nutritional Complications in Children with Neurological Impairment (NI) (2017), which was informed by a systematic review of the literature and expert consensus methods. Their statement about blended diet is '21f: ESPGHAN WG recommends caution if pureed food is used for enteral tube feeding in children with NI, because of concerns regarding nutritional adequacy and safety.'(10) Importantly, it was acknowledged in these guidelines that the evidence for this statement is low and further research is likely to have an impact on this recommendation.

Despite the BDA's position that home-blended foods should not be recommended, they also highlight the duty of care that the dietitian has for the child and therefore have provided a toolkit for dietitians to support parents who have chosen this method of feeding (1). This toolkit also calls for research in this area with a specific need to understand:

- whether home-blended food reduces the incidence of gut failure in children with long-term gastrostomy feeding

- the cost implications of a home-blended diet
- the impact on growth of using a home-blended diet
- whether the risk of microbial contamination results in harm to the patient
- the validity of nutritional analyses applications

Why this research is needed now?

An increasing number of children in the UK are gastrostomy fed, often for prolonged periods of time. Within this population there is growing interest among parents to using home-blended diets (2, 3). However, there is a lack of robust research which has assessed the safety and effectiveness of a home-blended diet (6, 10).It is worth noting that this topic was also in the top 40 research priorities for children with neurodisability in a recent James Lind Alliance research prioritisation exercise (11). The practice of using home-blended food is not likely to go away and it is very important that guidance and practice does not further develop in an evidence vacuum (4, 12).

The NIHR HTA programme have called for a two part study which includes a qualitative component and a prospective cohort study to examine risks, benefits and resource implications of using a standard formula diet compared to a diet of foods prepared and blended by the parent for children with long-term gastrostomies. We are proposing a 42 month study which offers value for money through ensuring appropriateness of outcomes and measurement tools, and using routinely recorded data where feasible to minimise primary data collection.

7. Aims and Objectives

Research Question:

What are the risks, benefits and resource implications for using home-blended food for children with gastrostomy tubes compared to currently recommended formula feeds?

Population: all children who receive all or part of their nutrition via gastrostomy tube.
Intervention: home-blended food via gastrostomy
Comparator: formula feeds via gastrostomy
Outcomes: symptoms, quality of life (QoL), anthropometric measures, nutritional intake, healthcare usage, complications

Objectives:

1. To identify the important outcomes of gastrostomy feeding for parents, young people and health professionals.
2. To assess the safety of home-blended diets for children who are gastrostomy fed compared to liquid formula diets.
3. To identify and quantify the benefits of home-blended diets compared to liquid formula feeds for children who are gastrostomy fed and their parents.
4. To identify and quantify the resources (family and statutory services) required to support home-blended diets compared to formula feeds.
5. To assess whether long-term follow-up of children who are gastrostomy fed is feasible using routine data sources.

Two work streams will address these objectives:

Work stream 1: a qualitative study involving young people, parents and health professionals will provide foundational evidence with regard to the design of Workstream 2 in terms of choice of outcome measures, other data to be collected, and the feasibility and acceptability of proposed data collection methods. It will gather data on young people's, parents' and professionals' desired outcomes of gastrostomy feeding, variability in diets and reasons for variation (e.g. respite facility may not accommodate home-blended feeds; oral feeding, reasons for, and perceived contribution to child's nutrition)(7); the perceived benefits of the

alternative diets, and patient safety issues experienced due to gastrostomy feeding and/or the diet used. Overall, WS1 contributes to study objectives 1-4.

Work stream 2: a cohort study of children who are gastrostomy fed including resource implications (objectives 1-4). We have also included a mechanism to assess the feasibility of long term follow up using routine data (objective 5).

8. Research Plan/Methods

Health technologies being assessed

For children who receive some or all of their nutrition via gastrostomies, diets of home-blended foods compared to prescribed liquid formula feeds will be assessed.

Workstream 1

Design

Qualitative research with purposefully sampled groups of young people, parents and healthcare professionals will investigate views on a number of topics relevant to informing final decisions regarding the design of the cohort study as well as generating 'stand-alone' evidence on young people's, parents' and professionals' views about gastronomy feeding and the use of home-blended diets. The latter will also offer some useful contextual data when interpreting and considering the implications of the findings from the cohort study. Individual interviews will be used to gather data from young people and parents. Focus groups will be used to collect professionals' views. A pragmatic approach has been chosen for the design of this workstream, taking account of its duration and resources available, but which will yield sufficiently rich data to fulfil the workstream objectives.

Sampling

We will recruit via general, community and specialist paediatric services and children's nutrition and dietetic services. These will be selected to represent the range of broad positions taken by services with respect to home-blended diets (supportive, neutral and unsupportive) as indicated by the relative frequency of use of home-blended diets.

Purposeful sampling strategies will be used to ensure that factors thought to impact or influence views or experiences are represented in the study sample (13).

For parents, we will sample for the following characteristics: child's diet, service's stance on home-blended diets, conditions where gastrostomies commonly used (e.g. cerebral palsy, neurodegenerative conditions, cystic fibrosis), child's age and feeding history characteristics (e.g. age gastrostomy was inserted, diet, and, complexity via level of dependency and learning ability) of the child.

Similarly, healthcare professionals will be purposively sampled to ensure representation of: profession (e.g. paediatricians, dieticians, speech and language therapists), expertise across a range of conditions, stance on home-blended diets, experience of supporting families to use home-blended diets.

For the young person sample (12-18 years), and given the study objectives and time constraints, we will restrict recruitment to young people without significant cognitive impairment. This will, to some degree, restrict the range of conditions represented. However, within this group, we will sample in terms of: duration of gastrostomy feeding, age, and type of diet.

Identification and recruitment of parents and young people

Young people and parents will be recruited via at least six services (~3 general community and specialist paediatric services; ~3 children's nutrition and dietetic services). Service staff will provide the research team with an anonymised list of potential study participants, detailing the sampling characteristics described earlier. The research team will review this information and, using the purposive sampling criteria, specify those individuals to whom they would like the service to pass on the study recruitment pack (letter of invitation,

study information sheet, response form, reply paid envelope) either in clinic or via post/email. If both young person and parent are to be approached, separate recruitment packs will be used. (For young people <16 years, the parents' information sheet will make reference to the fact that their child is also being invited to participate). Individuals interested in participating in the study will return the response form direct to the research team indicating their interest in taking part in the study. A member of the research team will then make contact, discuss participation further and, if agreed, make arrangements for an interview. The study information sheet will refer to the fact that a small 'thank you' gift (£20 shopping voucher for parents and young people age 12-18) will be sent to all those who participate in an interview.

Identification and recruitment of professionals

We will seek to recruit professionals working in three geographical areas, two of which will include services supportive of home-blended diets. Eligible health professionals based in community paediatric teams and tertiary treatment centres located within each area will be invited to attend a focus group discussion via letter or email. A study information sheet will be enclosed/attached with this invitation. We will manage and monitor recruitment so as to ensure all relevant professional roles are represented at each group by at least two individuals. Maximum group size will be 10 study participants. Convenient venues and times will be offered.

Target population

- Parents (n=20) of children and young people (aged up to 18 years) who are fed via a gastrostomy.
- Young people (n=5-10) aged 12-18 years currently using a gastrostomy and with no significant cognitive impairments.
- Health professionals, specifically paediatricians (n=6-8), dietitians (n=6-8), children's community nurses (n=6-8), and Speech and Language Therapists (n=6-8).

Data collection

Individual interviews (young people, parents) and focus groups (professionals) will be used to collect data. Individual interviews will typically be face-to-face, but parents will be offered the choice of a telephone interview. Consent will be recorded at the start of the interview/focus group. For young people aged 12- 15 years (inclusive), child assent and parent consent will be obtained. Young people aged 16-18 will be provide their own full consent.

Interview/focus group schedules will cover the following topics (tailored to the characteristics of the interviewee(s)):

- typical diet followed and factors which may affect adherence to that diet
- in terms of blended diets, factors influencing decision to use diet, types of food comprising diet, parental management of diet, support and guidance offered and adherence to guidance
- desired and observed immediate and longer-term health and quality of life outcomes (including unanticipated and/or undesirable) for the child of gastrostomy feeding and perceived impacts of the type of diet used;
- observed symptoms associated with gastrostomy feeding (e.g. reflux, constipation) and impacts of type of diet on symptoms;
- perceived outcomes for parents of their child being fed by gastrostomy, and impacts of type of diet on these outcomes;
- perceived/experienced risks/safety issues and other drawbacks associated with gastrostomy feeding, including the type of diet used;
- reported/perceived costs to families and the NHS (financial, time) of using gastrostomies and the impact of type of diet on those costs.
- views on the appropriateness, relevance and comprehensiveness of proposed outcome measures.

In addition, interviews with parents will explore views regarding feasibility and acceptability (in terms of parent participation) of the proposed design of the cohort study (for example, proposed recruitment methods, collecting nutritional data, respondent burden). To achieve this, prior to being interviewed, parent interviewees will be sent and asked to review and complete the parent-report data collection tools (including alternative options for measurement of gastrointestinal symptoms and quality of life) currently proposed for

use in the subsequent cohort study (see WS2 below). We will also ask parents about strategies to support retention to the cohort study.

For interviews with young people who have communication impairments, we will use their preferred communication systems and, if necessary, use or create visual tools (for example Talking Mats™(14)) to facilitate the interview (15).

With participants' permission, interviews/focus groups will be audio-recorded and verbatim transcripts obtained.

Data analyses

We will use thematic analysis techniques (16) to analyse the data to identify and describe experiences of gastrostomy feeding, ways in which blended-food diets are being implemented, outcomes that are important across the sample, resource implications and complications associated with blended feeds, and to examine the acceptability and appropriateness of piloted measurement tools.

Specifically, we will use the Framework approach (17) to facilitate systematic data management and ensure audit trails of the data management process. There are four stages to this process. First, researchers familiarise themselves with the data, and identify themes and key issues. Based on identified themes and any a priori issues (e.g. acceptability of proposed WS2 data collection tools), an index of themes is constructed (the thematic framework). Data are then indexed according to which theme(s) in the analytical framework they relate to. Finally, the indexed data from each case (e.g. participant, focus group) are summarised onto a series of thematic matrices (or charts). Each chart is divided into columns, allowing relevant data to be organised according to sub-themes/issues. A single row on each chart holds one participant's data. Thus reading along a row provides an overview of everything an individual spoke about in terms of a specific issue. Reading down the chart (or down a column) allows comparison between participants'. The final stage of analysis involves 'reading' of the charts, composing 'analytical notes' which describe the data and developing interpretation and hypotheses which are then tested against the charts and raw data. To start, data will be analysed by participant group after which there will be a process of comparison between groups.

Integrating WS1 findings into final decision-making regarding WS2

In Month 11, WS1 findings, and their implications for the proposed design of WS2, will be presented to the study steering committee (SSC) which will comprise experts / representatives from relevant stakeholders groups (see section 8). The SSC will be tasked, in discussion with the research team, with agreeing which outcomes to measure in WS2 and selecting appropriate measurement / data collection tools for these in terms of feasibility and comprehensiveness. If additional outcome domains are identified in WS1, candidate outcome measures will be identified by the research team and presented to the SSC. Selection will be informed by existing reviews of outcome measurement in the target population(s) (5, 18). The SSC will also review WS1 findings regarding the need to include further descriptive and predictor variables, and the team's proposed means of collecting data on these. In addition, findings regarding the acceptability and feasibility of the proposed design of WS2 (in terms of parent recruitment and supporting retention to the study) will also be reviewed by the panel and, in discussion with the research team, lead to final decisions being made about the overall design and execution of WS2.

Workstream 2

Design

A prospective cohort design with an initial 18 month follow-up period and including an assessment of the potential for a long term (10 years+) follow-up using routine data sources to measure key outcomes for these children.

The cohort study will run from months 6 to 42 of the overall study.

The initial 6 months of the study, whilst WS1 is underway, will be used to set up the prospective cohort study. The key processes that need to happen in this time period are:

- HRA research ethics and local governance approvals
- Identification of research sites (including looking at potential numbers of children in both diet groups and confirmation of participation)
- Study set-up in research sites, including training of healthcare staff in recruitment and data collection processes.

Sampling

Identification and recruitment (months 6-18): eligible children will be identified by research sites via the general community and specialist paediatric services, and children's nutrition and dietetic services. Due to the geographical variation in the use of home-blended diets (2), recruitment sites will be across England and purposively selected to ensure we include services where home-blended diets are, or are not, promoted. Sites which have confirmed their participation (subject to appropriate approvals) are:

Site	**Number of children with Gastrostomies**	**Number of children on blended diet**
Sunderland	70	5
Poole	50	~10
Children's Hospice South West	100	20
Manchester	150	~5-10
York	70	3
Birmingham Children's Hospital	100	15-20
Midlands Partnership Foundation Trust	30	1
Cambridge Community services	200	?
Birmingham Community trust	299	10
Walsall Healthcare NHS Foundation Trust	31	4
Shrewsbury and Telford NHS Trust	100-300	3
Hereford/Wye Valley Hospital	27	0
Dudley Group of Hospitals	50	8
Worcestershire Health and Care Trust	30	1
Leeds Community Trust	?	?
Evelina	~1000	50
Newcastle	300	30
Alder Hey		?
Nottingham		15-20
Portsmouth & Southampton (solent NHS trust)	137+102	14+ ?
Somerset	60	25

These services report having approximately 3000 children who are gastrostomy fed with ~230 children on blended diet We expect a recruitment rate of ~25% in children who are formula fed but more than 50% in those on a home-blended diet (based on discussions with these sites). We have included a children's hospice as a recruitment site in response to our PPI work. Formal recruitment of sites will be undertaken in the first 6 months of the study by re-contacting all potential sites.

We will also advertise the study on participating site websites and other relevant websites (e.g. charities, social media) where parents are likely to visit. Adverts will inform parents that they can only take part if their child is supported by a NHS service taking part in the study. Interested parents will be asked to contact the research team directly by email or telephone.

Target population

Sample Size: N~ 300. Given the large and growing number of children in England who have a gastrostomy (see background section) the proposed sample size of 300 is feasible. There are no robust data available on

the number of children in the UK who are fed a blended diet via gastrostomy; however, a survey conducted by Blended Diet UK, an online support group for parents/carers of patients who are fed home-blended diet, in 2014/15 identified 218 families using a blended diet. In addition, it would appear that there may be significant variation between localities in terms of the proportion of children who use blended diet (personal communication with paediatricians). Therefore, to ensure that we recruit an adequate number of children on a blended diet a large number of recruitment sites will be required (~21).

Given that no data are available on the exact proportion of formula fed vs home-blended diets represented in the study various scenarios need to be explored in terms of ensuring that the study would be adequately powered. Table 2 demonstrates the impacts of varying the number of children on home-blended diets in terms of adequacy of sample size.

Table 2: Sample Size calculation

No. in study	**Home blended**	**Binary**			**Continuous**	
		Estimate	**95% CI**		**SD**	**95%**
300	50	50%	±14%		20	±6%
300	60	50%	±13%		20	±5%
300	70	50%	±12%		20	±5%
300	80	50%	±11%		20	±4%
300	90	50%	±10%		20	±4%
300	100	50%	±10%		20	±4%
300	110	50%	±9%		20	±4%
300	120	50%	±9%		20	±4%
300	130	50%	±9%		20	±3%
300	140	50%	±8%		20	±3%
300	150	50%	±8%		20	±3%
300	50	60%	±14%		25	±7%
300	60	60%	±12%		25	±6%
300	70	60%	±11%		25	±6%
300	80	60%	±11%		25	±5%
300	90	60%	±10%		25	±5%
300	100	60%	±10%		25	±5%
300	110	60%	±9%		25	±5%
300	120	60%	±9%		25	±4%
300	130	60%	±8%		25	±4%
300	140	60%	±8%		25	±4%
300	150	60%	±8%		25	±4%
300	50	70%	±13%		30	±8%
300	60	70%	±12%		30	±8%
300	70	70%	±11%		30	±7%
300	80	70%	±10%		30	±7%
300	90	70%	±9%		30	±6%
300	100	70%	±9%		30	±6%
300	110	70%	±9%		30	±6%
300	120	70%	±8%		30	±5%
300	130	70%	±8%		30	±5%
300	140	70%	±8%		30	±5%
300	150	70%	±7%		30	±5%

From the table on page 14 we can see that with a sample size of 300 for the analysis (assuming there are twice as many formula fed as home blended) we should be able to estimate proportions within each group to within a margin of error of ≤10% and continuous measures (e.g. PEDSQL assuming standard deviation 20) to within a standard error of 4 points.

Inclusion/exclusion criteria

Population of interest/inclusion criteria: all children who receive all or part of their nutrition via gastrostomy tube

Exclusion criteria:

Children with a temporary gastrostomy.

Children aged over 18 years or < 6months old.

Children for whom a parent or legal guardian is not their primary carer (e.g. young adults in residential care)

Non-residents of England.

Appendix B provides the final inclusion and exclusion criteria employed for WS2, which were informed by WS1 findings and approved by the SSC.

Setting/context

Children who are gastrostomy fed can have a range of underlying diagnoses which include neurodisability, metabolic conditions, cystic fibrosis, cancer or cardiac disease. Their care will be coordinated by either a community paediatric service or tertiary specialists.

Recruitment and consent.

A staged consent process as set out below will be used for: i) consent to contact (consent for clinicians to provide details to research team); and ii) participation consent (consent to take part in the study through completion of questionnaire at baseline and follow-up, consent to share medical records data, permission for professionals to provide clinical information about the child; and permission to transfer patient identifiable data to NHS Digital to enable linkage to HES and ONS records for the purpose of the duration of this study and the next 10 years).

1. At a child's routine appointment (which may be held in person, by telephone or by video call) the study will be introduced by a member of the clinic team (dietician, paediatrician, specialist nurse) to the child/young person and parent(s). Where both the parent and child/young person express an interest in taking part in the study, documented consent to be contacted by the research team will be obtained.

The consent to contact form will include the following details: parent and child's (where possible) interest in learning more about the study; child/young person's name and age; type of diet (blended, mixed, formula); family contact details; convenient times to be contacted by the research team; name of clinician and date of their next routine appointment (which will be used for baseline data collection). For young adults (16-18yrs) an assessment of capacity, in line with the Mental Capacity Act, will be recorded by the clinician.

Eligible families who don't attend a clinic appointment during the recruitment period will either be contacted by telephone by an appropriate member of the local research team (e.g. clinician, research nurse) with documented consent to contact taken during the call, or sent a postal invitation from the recruiting NHS site and be asked to return a consent to contact form to the research team if they are interested in taking part. Families who respond to an advert will also be asked to complete a consent to contact form. Again, for young adults (16-18yrs) an assessment of capacity will be made by the clinician and recorded on the consent to contact form. For families who are posted an invitation, consent to contact may be obtained during reminder calls made by a member of the local research team.

2. On receiving completed consent to contact forms, the research team will contact families using their preferred method of communication to explain the study, and check the level of understanding and capacity of the child or young person and ascertain their wishes to provide their own data for relevant outcomes (e.g. self-reported quality of life). Assistance required for families to complete the study questionnaires will also be assessed during this initial contact.

3. A full study information pack will be posted or emailed to families (using their verified email address) who are still interested in taking part. This will contain relevant participant information sheets and study consent forms depending on the child / young person's understanding and capacity, and for postal packs a return envelope.
Information sheet versions:

- Child and young person (7-15yrs)
- Parent
- Young adults (16-18yrs)
- Young adults (16-18yrs) without capacity

For young adults (16-18yrs) who lack capacity, we will identify an appropriate personal consultee to provide advice about the young adult's views and wishes about taking part in the study, using appropriate consultee information sheets and consultee declaration forms. The full process for including adults without capacity is described in Appendix A of the protocol.

Families will be asked to complete the study consent forms (via email link using Adobe sign or on paper to return to the study team). Families will also be informed that they will receive the first study questionnaire within the following two weeks or around the time of their next clinic appointment if this is scheduled to take place within the following month. Consent processes are as follows:

- *Young adults age 16-18 yrs with capacity:* young adults and parents will provide separate consent for their own participation.
- *Young adults age 16-18 yrs without capacity:* no consent will be taken. Young adults will take part in the study if the consultee advises that they would not have any objections to taking part. Parents will consent separately for their own participation in the study.
- *Children and young people age 7-15yrs who can understand information about the study and express an opinion about taking part:* parents will provide consent and the child / young person will provide written or verbal assent (a simplified version of the assent / consent form will be used for children aged 7-11, with a standard version used for young people aged 12-15). Parents will provide separate consent for their own participation.
- *All other children and young people under the age of 16yrs:* parents will provide consent for their child and themselves.

Should any family not wish to take part after returning a consent-to-contact form, either by passively not returning the consent form before the end of the data collection period, or by actively agreeing not to take part, their details will be removed from our records and electronic / paper consent-to-contact forms will be destroyed.

<u>Data collection</u>

Baseline data collection

A baseline questionnaire will be provided as an online survey with a personalised link or a paper questionnaire, and for families who require assistance to complete this arrangements will be made (e.g. providing assistance by phone or visiting families to undertake data collection). As families are being recruited during months 6-12, this will take place between months 12-18.
After families complete their questionnaire, we will provide the clinician questionnaire to their child's clinician for completion.

The study will have three data collection time points: at recruitment (baseline) and then at 12 and 18 months. A small incentive voucher of £20 will be provided to each families after return of the questionnaires at each time point. At each time point, data on a range of outcomes as well as relevant clinical and feeding information will be collected from parents/children/young people and clinicians. These are detailed below.

Key outcomes

We would note that a recently completed review of health-related outcomes for children with feeding tubes and neurological impairment identified 120 unique outcomes and the authors concluded that a core outcome set was required to reduce heterogeneity in the measures being used by studies (19). Work on this core outcome set is still underway but if it is completed before the start of the proposed study we would incorporate the outcome set into the study design, and explore the acceptability and feasibility of measuring them in WS1.

The outcomes we currently propose to use are set out below, but note that they are subject to change dependent on WS1 findings. At this point, our selection of outcome measures has been based on:

- the commissioning brief and rapid review of the evidence (6);
- consultation with: dietitians, paediatricians, care team staff at a local children's hospice, a parent who currently feeds her son a blended diet;,
- information contained in the risk assessment of enteral tube administration of liquidised diet from the Parenteral and Enteral Nutrition Group (20), and the Practice Toolkit for liquidised food via gastrostomy tube from the British Dietetic Association (1).

Appendix C provides the final set of outcomes and variables to be included in WS2, informed by WS1 and decided by the SSC.

1. **Gastrointestinal symptoms:** There is no measurement tool for this population that has been validated for the whole age range included in this study. PedsQL™ Gastrointestinal Symptoms Module has been shown to identify children with functional and organic gastrointestinal disease but only in those aged over 2 years (21). Parent and child reported (from age 5) versions are available. However, it is long (58 items) and may need to be simplified. An alternative is a shorter symptom checklist used in a previous study in this population (22). Both will be reviewed by parents and young people in WS1.
2. **Quality of Life of the child**: Concerns have been raised about the suitability of generic paediatric QoL tools for this population of children as they may not measure all the factors relevant to their QoL. There are two alternatives: PedsQL generic module (23) and a previously developed questionnaire for this population that has attempted to quantify symptomatology and QoL in these children (22). For both, parent and child-report versions are available. Both will be reviewed by parents and young people in WS1.
3. **Parental QoL**: EQ5D is a standard QoL tool (24) and will be used in the economic evaluation. We also propose to include a more specific tool that measures psychological wellbeing in parents of children with disability (Parenting Morale Index (PMI)) (25). We will seek parents' views regarding the acceptability and meaningfulness of these measures in WS1.
4. **Dietary Intake:** The myfood 24 dietary assessment tool (www.myfood24.org) is an online food recall and diary system which has been developed by academics and validated against a suite of 'gold standard' reference measures of dietary biomarkers (26, 27). This tool will be piloted with parents in WS1 and adapted where necessary to reflect children's diets (e.g. extending the database to include relevant home-made and commercial products and supplements). Testing has shown that to record a full day dietary intake takes ~12 minutes. Collecting four days' worth of nutritional intake data has been shown to be the optimal time period (28). The nutritional content of formula feeds will be collected from the dietitians via the company product data.
5. **Anthropometric information:** weight, height/length, body mass index, mid upper arm circumference, multiple skin folds. Having longitudinal, multiple anthropometric data will allow assessment of appropriateness of weight gain or loss and distribution of body fat.
6. **Healthcare usage:** We will generate a version of the Client Service Receipt Inventory (29) to capture, via parental report, use of health services (e.g. appointments with paediatric and dietetic teams; emergency hospital admissions, GP attendance, A&E visits). We will collect these data at baseline for the previous 12 months in order to estimate the pattern of primary and secondary care resource use. We will then collect these at 12 and 18 months follow-up. We will also request the previous 2 years of Hospital Episodes Statistics (HES) data for each child to explore the potential of using routinely collected data for long term follow-up of secondary care usage and to assess recall bias in parental reporting.
7. **Safety outcomes:** Parental report of tube blockages, A&E or hospital visits to unblock or replace the device, parental report of gut or stoma site infections (including antibiotics prescribed by GP), and parental report and HES data on admissions to hospital or A&E attendances.

8. **Resource use associated with intervention or control:** Data collected on financial and time resource use will be informed by WS1 findings. We anticipate the following sorts of information will be collected:
    a. Parent: time taken to prepare feeds, impact of food preparation time on other care/parenting responsibilities, and, for parents using home-blended diets, any additional/unusual spending on food and food storage, cost of blender and any other food processing equipment purchased with respect to using a home-blended diet.
    b. Clinician: cost of formula and packaging for formula, dietetic resources.

Additional data items that will be collected include:

Feeding and diet: gastrostomy duration, blended/formula/mixed feeding (and history of feeding), bolus or overnight feeding, any oral feeding,

Demographic information: child age, gender, ethnicity, postcode to allow linkage to deprivation status (index of multiple deprivation), household composition (including number of dependent children), parental educational attainment (as a measure of socioeconomic status).

Clinical Information: primary diagnosis, co-morbidities, all medications and complexity (30, 31). Having detailed clinical information at baseline will allow us both to adjust for potential confounding factors in the analyses but also explore the possibility of undertaking subgroup analyses (e.g. by age or diagnosis group) if appropriate.

Data sources
At each time point, data will be collected directly from parents (PA), children (C; where appropriate), paediatricians (P) and dietitians (D). To minimise the burden on clinical teams, we will rely where possible on information recorded in the child's medical record, and utilise other members of the local research team to extract this (e.g. a research nurse).
We will use routine outpatient appointments where possible to collect the anthropometric measures to reduce the burden on participating families (32) and support study retention, using the most recently recorded measurements for each data collection point. Due to variation in timings and delivery of appointments, we will also ask parents to record these if possible.
The majority of the data will be collected via questionnaires administered according to participants' preferences (postal vs on-line; parents and young people will also be offered telephone interview). Parents choosing to complete paper questionnaires will be required to provide dietary information via the online myfood 24 tool or via telephone call with the research team who can complete this. Paper questionnaires will include the weblink and a QR code to this tool. Up to three reminders via text and/or post will be used at each time point.

Finally, we will use routine healthcare data through linkage undertaken by NHS Digital to the Hospital Episodes Statistics (HES) data (inpatient, A&E, outpatient) and the Office for National Statistics (ONS) death certificate data. We will request NHS digital to supply data from two years prior to study recruitment in order to obtain information on previous admissions or A & E visits due to infections, tube blockages and gastrostomy replacements/revisions. This is important as these children often have morbidity related to their gastrostomy feeding (33). The linkage to HES data will be undertaken by NHS Digital using their standard deterministic linkage methodology which uses NHS number, date of birth, gender and postcode. The linkage to the ONS data will also be undertaken by NHS Digital but that linkage can use first name and surname as well as NHS number, date of birth, gender and postcode.

Appropriate consent will be taken from the parent/young person that clearly states that in order for this linkage to be undertaken the research team will have to securely transfer their personal information to NHS Digital. This is important to gain the appropriate approvals from Independent Group Advising on the Release of Data (IGARD), the body which approves data linkages and releases from NHS Digital. The University of York has a current Data Sharing Framework with NHS Digital under which the Data Sharing Agreement for this study would sit and the Department of Health Sciences at the University of York has the appropriate data security approvals in place to hold and process HES and ONS data. Although over the last few years there have been significant delays for researchers and other organisations accessing data from NHS Digital (and its predecessor HSCIC). Their standard operating procedures state that their service works to a 60 working day turn around - for complex requests, including identifiable data across a series of datasets. They publish up

to date mean and median times for applications for research and currently the median time is less than 50 days (34). A provisional summary of data to be collected at each time point is provided in Table 3. Appendix C lists the agreed set of outcomes and variables to be included in WS2, as informed by WS1 and decided by the SSC.

Table 3: Data to be collected

Variable	Type of Variable	Proposed Measure	Source	Timings of data collection (months)		
				0	12	18
Participant characteristics / predictors						
Age		Date of birth	Parent	√		
Ethnicity		Census groups	Parent	√		
Deprivation		Index of Multiple Deprivation (based on postcode)	Parent	√	√	√
Parental educational attainment		Census groups	Parent	√		
Household composition		Number of children, marital / living status	Parent	√	√	√
Diagnosis			Paediatrician	√		
Co-morbidities			Paediatrician	√	√	√
All Medications			Paediatrician	√	√	√
Complexity		Disability Complexity Scale	Paediatrician	√	√	√
Length of time gastrostomy fed at T0		Months/years	Parent	√		
Comparator						
Diet: Formula/blended/ mixed	Main grouping variable		Parent	√	√	√
Outcomes						
Nutritional content of feeds	Outcome	Commercial for formula	Dietitian	√	√	√
		Myfood24 for blended	Parent	√	√	√
Anthropometric data	Outcome	Height or length Weight Triceps skinfold thickness or mid arm circumference	Dietician Paediatrician	√	√	√
Gastrointestinal symptoms	Outcome	PedsQL Gastrointestinal or other QoL questionnaire	Parent/ child	√	√	√
Child Quality of Life	Outcome	PedsQL generic module	Parent/ child	√	√	√
Parental Quality of Life	Outcome	EQ5D5L Parenting Morale Index	Parent	√	√	√
Healthcare use	Outcome	Client service receipt inventory	Parent	√	√	√
	Outcome	No. hospital admissions No. A and E attendances	HES data	√	√	
Safety	Outcome	Tube blockages No. of infections stoma No. of gastrointestinal infections	Parent			
	Outcome	Number of hospital admissions and A and E attendance associated with child's gastrostomy/diet	HES	√	√	
Family resource use	Outcome	Time preparing feeds; impact on other caring/parenting Financial costs	Parent	√	√	√

Non-staff NHS resource use	Outcome	Cost of formula and packaging Dietetic resources	Dietitian	√	√	√

Data analyses

The data quality of each data item collected will be assessed when the data is collected or received by the research team. Appropriate attempts will be made to obtain missing or out of value data. A review of the collected data will be undertaken after the first 25 participants have been recruited to check for any systematic issues with the data collection.

A statistical analysis plan will be developed and signed off prior to analysis. Analysis will follow STROBE (35) and RECORD (36) guidelines. Descriptive statistics of clinical and demographic characteristics of the study population at baseline will be used to examine differences between the groups of children who are predominantly formula fed and those who use home-blended diets.

Children will be grouped into those who are on a blended diet or formula diet at baseline by:

- Home-blended group if most of their nutritional intake is provided via home blended diet. This categorisation will be informed by WS1 and in consultation with the SSC.
- Formula fed if most of their diet comes from formula.

See Appendix C for final categorisation of groupings.

Most of the outcome measures will require scoring or aggregation before the statistical modelling can be undertaken:

- The Peds QL generic scale and PedsQL Gastrointestinal symptoms module will be scored as per the guidelines and transformed to a score of 0-100.
- The height (or length) and weight will be used to calculate an age and sex adjusted body mass index (bmi sds).
- The myfood24 data programme analyses the nutritional content the home-blended diet and will compute the calorie intake and the macro and micro nutrient content of the feed. The same data for the formula fed group will have been obtained, via the dietitian, from the commercial supplier.
- The parent reported number of site infections and other tube related complications will reported as total counts for each child.
- The diagnostic (ICD10) and procedural codes (OPCS) in the HES data will be used to identify admissions which were related to complications of the gastrostomy tubes or infections. The number of admissions and A and E attendances will be calculated for each child. Length of stay for each admission will also be calculated for the resource use analyses.
- Parent quality of life: the EQ5D VAS is scored 0-100 and the 5 component scale of the EQ5D-5L will be converted to a single score using a UK specific value set (37) . The 10 item Parenting Morale Index is scored from 0-100.

For all outcomes we will report the baseline score, follow-up score and change score.

Assessing safety (objective 2) and benefits (objective 3):

Assessing the safety and benefits of blended diet will be assessed using multivariable regression analyses. The type of regression will depend on the outcome of interest; logistic (tube blockage, appropriate nutritional content; yes/no), linear (PEDSQL gastrointestinal module score, BMI sds or upper arm circumference, calories, PMI, EQ5D), Poisson or negative binomial (number of A & E or hospital admissions for infections or complications of gastrostomy tube). Each analysis will account for the multiple confounding factors in this population (age, underlying diagnoses, comorbidities, outpatient attendance, parental factors, socio-economic status) and the main covariate of interest will be feeding status (blended vs formula). Study site will be added as a random effect to the models to allow for site level variation. Estimates and 95% CIs will be reported from the regression model for each outcome measure. The flow of participants through the study will be detailed including the number of individuals contributing to each analysis. The amount of missing data will be summarised for each outcome measure and multiple imputation will be used to assess the robustness

of the results. Results will be compared to the complete case analyses and important differences discussed. Sensitivity analyses will be considered to explore departures from the MAR assumption.

Measurement of cost and outcomes (objectives 3 and 4)

There is a lack of robust evidence around the cost-effectiveness of alternative feeding formulae for gastrostomy fed children. To address this, we will describe the costs and outcomes for those who use formula feed and those who use home blending (addressing objectives 3 and 4). The formula feed group will act as the treatment as usual.

Generating cost estimates

Unit costs for healthcare interactions will be collected from published sources (for example, PSSRU Unit Costs of Health and Social Care) and applied to the relevant resource use. The costs of healthcare interactions will be calculated by the product of unit cost and resource use analyses.

The unit cost of non-healthcare interactions, including the cost of the blended diet constituents and time taken to prepare will be estimated separately using published estimates where feasible. Resource use will be collected via questionnaires to parents and routine data. Sensitivity analyses will be conducted where alternative assumptions would generate substantially different cost estimates (for example, if there are substantial differences between parental report and HES data).

Generating estimates of Outcomes

We will describe and summarise estimates of parent changes in HRQoL (EQ5D-5L) and child (either PEDS QL or QoL questionnaire (22)). We will describe these for both groups within the cohort.

We will report total costs, mortality and adverse event rates associated with both home-blended and formula feeds in a cost-consequences framework.

Long term follow up (objective 5)

The utility of routine data sources as an option for long term follow up of study participants will be assessed by examining the concordance between parent reported data on A and E visits and hospital admissions due to infections or complications of their gastrostomy tube with HES data for the corresponding time period. Concordance will be assessed using the kappa statistic both for the total sample and separately by the home-blended and formula fed groups.

If there is concordance between the parental reported infection and gastrostomy related healthcare usage and HES data, long term follow-up would be possible by obtaining further extracts of HES data and ONS death certificate data. The HES data will provide information on admissions and A&E visits due to infections and complications of the gastrostomy (blockages, revisions, replacements). The ONS data will provide date and cause(s) of death if the child has died.

We would also note that the mandated NHS Community Services Data Set (38) has recently started collecting data on children with disabilities and is another potential source of long term follow-up data. This dataset contains more detailed information on the child's underlying conditions, management including use of medical technologies and outcomes. The status of that dataset will be clearer towards the end of this project (at which point it will have been implemented for over 5 years): we will therefore review its potential 6 months prior to the project end date by assessing the number of trusts submitting data and the completeness of these data

9. Dissemination Plan

The results of WS 1 and 2 will be integrated into the final report and the other outputs of this study. A Parent Advisory Panel (see Section 14) will assist with the content and format of parent/child facing outputs.

Outputs:

- Professional resources;
    a. a text-based research briefing, setting out key findings and implications for practice

    b. a multi-media presentation for use in multi-disciplinary team meetings and as an individual learning resource.
    c. a summary for commissioners.
- A summary of findings presented in a way that is meaningful for parents and children and young people.
- The final report for the NIHR HTA journal.
- Two manuscripts for submission to peer-review journals (open-access).

All outputs will be available from the study website and highlights from key outputs will be disseminated through professional and parent networks. A QR symbol will appear on all outputs linking the reader to all other project outputs.

10. Project timetable

A detailed timeline, with key milestones and deliverables is shown on page 24. This will be updated regularly in line with study progress and revised where required.

Abbreviations: PAP Project Advisory Panel, SMT study management team, SSC Study Steering Committee, HRA Health Research Authority

Project: The role of different diets in children who are gastrostomy fed

YEAR 1	Feb-19	Mar-19	Apr-19	May-19	Jun-19	Jul-19	Aug-19	Sep-19	Oct-19	Nov-19	Dec-19	Jan-20
WS1												
HRA Approvals												
Site set-up												
Obtain PEDS-QL licence												
Recruitment of Professionals												
Undertake Professionals Focus Gps												
Recruitment of Parents & Young People												
Undertake Interviews of Parents and Young People												
Transcription & Analyses												
WS2												
HRA Approvals												
Recruitment Grade 5 post												
Initial contact with Sites												
Apply to NHS Digital for access to HES/ONS data												
Study Site setup												
HRA Amendment (if necessary)												
Recruitment												
Governance												
SMT meeting												
PAP meeting												
SSC meeting												
Milestones												
HRA approval obtained												
Recruited required no. of professionals												
WS 1 Recruited required no. of parents												
WS 1 Recruited required no. of young people												
WS 1 analysis pertaining to WS2 design complete												
Final list of outcomes/tools												
Progress Report												

YEAR 2	Feb-20	Mar-20	Apr-20	May-20	Jun-20	Jul-20	Aug-20	Sep-20	Oct-20	Nov-20	Dec-20	Jan-21
WS1												
Prepare paper reporting WS1 findings												
Submit paper reporting WS1 findings												
WS2												
Recruitment												
Baseline data collection												
Apply to NHS Digital for access to HES/ONS data												
Newsletter												
9 month data collection												
Governance/Reporting												
SMT meeting												
PAP meeting												
SSC meeting												
Milestones												
NHS Digital application submitted												
NHS Digital approval obtained												
Receipt of first HES data												
Recruitment Target hit												
Baseline data collection completed												
Progress Report												

YEAR 3	Feb-21	Mar-21	Apr-21	May-21	Jun-21	Jul-21	Aug-21	Sep-21	Oct-21	Nov-21	Dec-21	Jan-22
9 month data collection												
Final data collection												
Apply to NHS Digital for 2nd cut of data												
Preliminary analyses												
Newsletter												
HES cleaning/analyses												
final data analyses												
resource use analyses												
Governance/Reporting												
SMT meeting												
PAP meeting												
SSC meeting												
Milestones												
9 month data collection complete												
Final data collection complete												
Progress Report												

YEAR 4	Feb-22	Mar-22	Apr-22	May-22	Jun-22	Jul-22
WS2						
HES cleaning/analyses						
final data analyses						
resource use analyses						
Newsletter						
Governance/Reporting						
SMT meeting						
PAP meeting						
SSC meeting						
Milestones						
Receipt of 2nd HES extract						
All analyses complete						
Final Report						
Manuscript submission						

Complete
To achieve

11. Patient and Public Involvement

A parent of a child who is fed a home-blended diet has commented on the research design and application, and provided input on the plain English summary. We undertook further parent consultation with our Martin House Research Centre Family Advisory Board. This meeting was attended by 10 parents including parents of children with a range of life-limiting conditions and/or medical complexity, bringing expertise by experience about caring for a child with complex healthcare needs and liaising with multiple healthcare professionals. Five parents had experience of gastrostomy feeding with a mixture of formula and home-blended diets. We discussed branding of this study to encourage participation, recruitment methods and parental involvement. Further to this involvement we have added discussing recruitment methods in WS1 and changed the title of the study.

Two parents of children who are currently feeding their children home-blended diet and one other parent have expressed that they would be interested in being members of the Project Advisory Panel (see below).

We will establish a Project Advisory Panel consisting of parents, carers and young people via existing consultation groups which are facilitated by the applicants and their networks. We will recruit additional parents and young people to ensure a mix of families that use home-blended and formula feeds. The panel will meet twice per year to provide input on the study. Due to the busy and unpredictable lives of these families some consultation work will be virtual. Members will receive reimbursement for their role according the INVOLVE guidelines.

Members of the panel will be involved in the following:

Study management: A minimum of two members of the panel will also be members of the Study Steering Committee. They will be supported in their role.

Developing study materials: Participant information leaflets, consent forms and interview schedules for the study will be developed in consultation with the Project Advisory Panel.

Study design: input on the acceptability and feasibility of the measurement tools.

Study reporting: Members of the panel will help to produce information resources for parents, children and young people at the end of the study.

Dissemination: The Project Advisory Panel will help to identify routes for dissemination and assist in the dissemination of the study outputs directly via their own networks.

12. Roles and Responsibilities of the Project Team

Dr Lorna Fraser (CI) will coordinate this study and lead WS2.
Professor Bryony Beresford will lead WS1.
Professor Gerry Richardson will lead the economic aspects of the study
Professor Catherine Hewitt will oversee the overall study design and the statistical analyses in WS 2.
Dr Johanna Taylor will manage the day to day running of WS2.
Professor Janet Cade will provide input to the use of the myfood24 product and the nutritional assessment component of WS2.
Dr Karen Horridge will provide clinical input and inform the dissemination strategy via links to the BACD and the RCPCH.
Alison McCarter will provide clinical expertise to the study and will also inform the dissemination strategy via her links to the BDA.

13. Oversight Committees

Study Management Team

This include all co-investigators and the staff working on this study. They will meet every two months to discuss recruitment, targets and general progress. The SMT will produce reports for the study steering committee.

Independent Study Steering Committee

This committee will comprise of an independent chair and representation from paediatricians, dietitians, speech and language therapists, parents/carers (to represent the Project Advisory Panel members), appropriate national disability charities (Council for Disabled Children, Together for Short Lives), parent organisations (e.g. National Network of Parent Carer Forums, Contact) and professional bodies (British Academy for Childhood Disability, British Dietetic Association and the Royal College of Paediatrics and Child Health). This panel will meet twice a year to assess progress of the study against the defined milestones and deliverables and provide advice and expertise to the Study Management Team.

14. Ethics and Regulatory requirements

Regulatory Compliance

The study will comply with the principles of the Declaration of Helsinki (World Medical Association, 2013). It will also be conducted in compliance with the approved protocol, and the principles of GCP. The sites will comply with the principles of GCP and applicable national regulations, including the MCA (Department of Health, 2005). An agreement will be in place between the site PI and the Sponsor, setting out respective roles and responsibilities.

Ethical Considerations

This study involves a longitudinal data collection from children with serious health conditions and families which does raise several ethical issues.

Informed consent: the consent process is detailed on page 15-16 of this protocol. The parent and child (where appropriate) will be given adequate time to ask questions and read information about the study before they consent to participation. It will be made clear on the information leaflets that there is no obligation to participate in this study and that the clinical care of their child will not be influenced if they choose not to participate. It will be also made clear that participation in the study does not require the child to remain on the same diet during the study period.

Confidentiality All data generated by this study will be anonymised and securely stored in the Department of Health Sciences at the University of York. Personal data will be stored separately from the other study data in a restricted folder which will be password protected and only accessible by members of the research team. This will include scanned copies of the consent forms. Due to the potential long-term follow-up for this study these data will be retained for a minimum of 10 years. This study will comply with the new General Data Protection principles and the Research governance framework for Health and Social Care Research. All information from this study will be kept confidential.

Participant Burden We wish to recruit families with children with high healthcare needs who often lead very busy and unpredictable lives. We have attempted to keep the participant burden to a minimum by obtaining data via routine clinical appointments and by supplementing primary data collection with routinely collected data. All participants will be informed in the information leaflets that they can withdraw from the study at any point time.

Supporting Families
Families who have consented to participate in this study will be supported through the study processes by the research team. They will be provided with contact details of the research team and contact can be made via text message, phone call or email. Telephone or face-to-face support from a member of the research team will also be offered when required to complete study questionnaires.

Families raise questions about their child's diet with the research team If a parent asks the research team for advice about their child's diet or wider care, the response of the team will always be to advise the parent to discuss with the appropriate professional involved in their child's care. We will also ensure that all family facing information about the study is presented in a balanced way that does not suggest a preference for one diet over another.

Child death Research sites will be asked to inform the research team if a child dies during the study period. This should prevent the research team from contacting the family further if a child has died.

Ethical Approval

Formal NHS Research Ethics Committee (REC) approval will be sought via the Health Research Authority (HRA). Local R&D approvals (Confirmation of Capacity and Capability will be obtained for participating sites. Any further amendments to the trial protocol will be submitted and approved by the HRA and REC where required. Annual reports will be provided to the ethics committee and the ethics committee will be notified that the study has ended, within 90 days.

15. Funding

This study is funded by the National Institute for Health Research Health Technology Assessment programme (ref 17/76/06). This was a commissioned call so the funder identified the topic area for this study but will have no role in the study design, data analyses or conclusions in this study.

16. Indemnity

As the Sponsor, the University of York includes provision of standard public liability insurance to meet the potential legal liability of the sponsor for harm to participants arising from the design and management of the research. To meet the potential legal liability for harm to participants arising from the conduct of the research, standard NHS indemnity will apply for participants recruited from NHS sites and University of York public liability insurance will apply for participants recruited from non-NHS sites (e.g. children's hospices).

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Appendix A – Process for involving young adults (16-18) who lack capacity

STEP 1: ASSESSMENT OF CAPACITY

A large proportion of young adults (age 16-18) who will be eligible for inclusion in the study will have an impairment of, or disturbance to, the functioning of the mind or brain due to their underlying condition. Therefore for all young adults who are eligible an assessment of capacity will be made by the recruiting clinician, who will be known to the young adult and involved in decisions about their care and treatment. In line with the Mental Capacity Act 2005 (MCA) the assessment will be undertaken in two stages so that the principle of assumed consent will be upheld for young adults who do not have a cognitive impairment / disturbance:

1) The clinician will be asked if the young adult has an impairment of, or disturbance to, the functioning of the mind or brain
Only if this is the case:
2) The clinician will be asked to assess if the impairment or disturbance means that the person is unable to make a decision about whether or not to take part in the study

For young adults who are recruited during a clinic appointment or by post
Clinicians will be asked to make an assessment of capacity at the time of completing the consent to contact form with families during a routine appointment. This will be recorded in Section 4 of the consent to contact form, which will be completed by the clinician after parents and where appropriate young people complete Sections 1-3.

For families who are invited by post (e.g. those who miss a routine appointment during the study recruitment window), parents will complete the same consent to contact form, which will then be shared with the child's paediatrician (who will be named on the form) to complete Section 4.

For young adults of families who respond to an advert about the study
In all of these cases parents will be asked to complete a brief consent to contact form giving us their permission to share the form with their child's paediatrician, who will be named on the form. This will also contain a section for clinicians to complete about the young adult's capacity. The research team will organise this with the child's paediatrician.

STEP 2: IDENTIFYING A PERSONAL CONSULTEE

From our experience with this population, the consultee is likely to be the young adult's parent / legal guardian in the majority of cases. However, there may be a small number of cases in which another person (e.g. adult sibling, paid carer) is the young adult's carer (rather than their parent) and is the appropriate consultee for the study. There may also be instances, (although from our experience this is very unlikely), in which another person is the consultee but the parent is the primary carer.

This study is specifically examining parent quality of life and burden as well as child outcomes, requiring participation of a child/ young person and their parent. The study will therefore not include young adults who lack capacity whose parent is not their primary carer.

To identify any young adult whose main carer is their parent but whose consultee is someone else, the clinician who assesses capacity will also be asked to indicate whether someone other than their parent is the appropriate personal consultee (on Section 4 the consent to contact form).

In cases where the personal consultee is someone other than a parent, the recruiting service will write to the consultee to invite them to act as a consultee for the young adult, explain what this means and make clear it is entirely their decision. The personal consultee will be asked to return a consent to contact form to the research team if they are happy to take on this role, or to contact them directly by email or telephone. A

project leaflet will be included with the invitation letter so that they understand what the study is about when making a decision about whether to act as the young adult's consultee.

If the person identified as the young adult's personal consultee is not available or willing to act as their personal consultee for the study, the research team will liaise with the young adult's paediatrician to identify another personal consultee. If no-one can be identified the research team will again liaise with the young adult's paediatrician to identify a suitable 'nominated consultee' (e.g. paid carer, specialist nurse, dietitian, social worker, teacher) who knows the young adult well but is independent to the research.

STEP 3: PROVIDING INFORMATION

The research team will contact consultees by telephone to explain more about the study and their role. In most cases this person will be the parent who will also take part in the study, so this conversation will happen at the same time as the initial phone call about their own participation following consent to contact. Following this, consultees will be posted a Consultee Information Sheet (which will include the same level of information that the participant would receive if they had capacity), a Consultee Declaration form to record their advice, and a pre-paid envelope to return this. For parents we will use a brief Consultee Information sheet that outlines their role as consultee and references their own PIS, which contains all the information about the study that a young adult would receive if they could decide for themselves.

Young adults who can understand information about the study (which we will ascertain from their consultee) will receive a simple version of the Participant Information Sheet which tells them why the study is being carried out, why they have been invited, what will happen if they take part including any risks associated with this, and what will happen to their information.

STEP 4: SEEKING ADVICE FROM THE CONSULTEE

Consultees will be asked to provide an opinion on the views and feelings they believe the adult would have towards participation in the study. If they feel that the young adult would have no objection to taking part in the study, they will be asked to record this on the Consultee Declaration form and return the completed form to the research team. Young adults for whom we receive a completed Consultee Declaration form will take part in the study. We will liaise with the consultee during this process to ensure they are encouraged to complete and return a consultee declaration form in cases where they feel that the young adult has no objections.

STEP 5: SEEKING ONGOING ADVICE FROM THE CONSULTEE

Workstream 2 involves three data collection points (baseline, month 12 and month 18). To ensure that participants' views and feelings throughout the study are taken into consideration we will contact each young adult participant's consultee by telephone prior to collecting data at month 12 and month 18 and check whether the young adult's views may have changed, and whether the young adult should remain in the study. Young adults will be withdrawn from the study if the consultee believes this reflects the participant's views and feelings about continuing their participation.

If a participant's consultee is no longer available at these data collection points we will make steps to identify another personal / nominated consultee to undertake this role. In these cases, we will liase with the participant's paediatrician to identify an appropriate consultee.

The research team will keep a record of on-going communication with young adult participants' consultees and any changes during the study.

Appendix B – Final inclusion and exclusion criteria for WS2

	ELIGIBLE	***INELIGIBLE***
A	Child is at least 6 months old and under 19 years	Infants up to 6 months and young people who are 19 years and older
B	Child is gastrostomy feed dependent	Child has another type of feeding tube (e.g. nasogastric, jejunostomy)
C	Child receives most or all of their nutrition via the gastrostomy	
D	Child is living with parent(s): biological or adoptive	Child is not living with a parent (e.g. in residential setting or foster care)
E	Family resident in England	Family not resident in England

Appendix C – Definitive list of outcomes and variables to be collected in WS2

Variable	Proposed Measure	Source				Timings of data collection (months)		
		Parent	Child	Clinician	HES Data	0	12	18
Comparator								
Diet: Formula and Blended	Formula only vs. blended only or mix of formula / blended	☑		☑		☑	☑	☑
Blended feed proportion	Percentage of diet from blended feeds	☑						
Outcomes – gastrointestinal symptoms								
Gastrointestinal symptoms	PedsQL GI Symptom Scales plus two new items about retching and gagging (wording adapted from Zaidi et al., 2010)[22]	☑	☑			☑	☑	☑
Gastrointestinal medications	Number of each GI medication (antacids, prokinetics, antispasmodics, laxatives, H2 blockers, anti-sickness medications, proton pump inhibitors, other)	☑		☑				
Outcomes – life impact								
Child quality of life	DISABKIDS Chronic Generic Short Version (12 items)	☑	☑			☑	☑	☑
Child physical health state	EQ-5D-Y Visual Analogue Scale	☑	☑					
Child sleep	PROMIS® Paediatric / Parent Proxy Sleep Disturbance – Short Form 4a	☑	☑					
Child comfort	How comfortable is your child generally? (from Zaidi et al., 2010)[22]	☑						
Child social participation	Nursery / pre-school / school / college absence (I miss school because of not feeling well; I miss school to go to the doctor or hospital (from PEDS-QL generic core scale))	☑	☑					
Parent quality of life	EQ-5D-5L, Parenting Morale Index	☑						
Parent sleep	PROMIS® Adult Sleep Disturbance – Short Form 4a	☑						
Parent anxiety	EQ-5D-5L anxiety / depression dimension	☑						
Time associated with gastrostomy feeding	Minutes per day to prepare feeds; prepare medications; administer feeds; administer medications; do gastrostomy care (e.g. flush tube, clean site)	☑						
Ease of gastrostomy feeding	How easy is it to feed your child? How easy is it to administer medications to your child? (adapted from Zaidi et al., 2010)[22]	☑						

Variable	Proposed Measure	Source				Timings of data collection (months)		
		Parent	Child	Clinician	HES Data	0	12	18
Outcomes – growth and development								
Nutritional intake	Nutritional content of formula prescription (type and amount); prescribed dietary supplements; blended or oral feeds (3-day food diary – parents only)	☑		☑		☑	☑	☑
Height or length	Most recent recorded (cm)	☑		☑				
Weight	Most recent recorded (kg)	☑		☑				
Body mass index	Calculated from height and weight							
Mid-upper arm circumference	Measured with a MUAC tape measure provided by study team (mm)	☑		☑				
Outcomes – safety**								
Tube blockages	Number of blockages; number of blockages requiring hospital treatment*	☑			☑	☑	☑	☑
Tube malfunctions	Number of replacements; number of replacements requiring hospital treatment*	☑			☑			
Stoma site infections	Number of infections; number requiring treatment (antibiotics or hospital treatment)*	☑			☑			
Gastro-intestinal infections	Number of infections; number requiring treatment (antibiotics or hospital treatment)*	☑			☑			
Aspiration pneumonia	Number of times; number requiring treatment (antibiotics or hospital treatment)*	☑			☑			
Death	Date and cause of death			☑				
Outcomes - healthcare use and cost***								
Hospital admissions	Number, duration and type of admissions*	☑			☑	☑	☑	☑
A&E attendance	Number of attendances*	☑			☑			
Outpatient appointments	Number of appointments with paediatrician, community nurse, dietitian, speech and language therapist*	☑						
GP appointments	Number of GP visits*	☑						

Variable	Proposed Measure	Source				Timings of data collection (months)		
		Parent	Child	Clinician	HES Data	0	12	18
Outcomes - cost of feeds								
Cost to families – blended feeds	Type of feeds given and proportion (blended family meal; blended meal prepared for child; purchased blended feed (e.g. pureed vegetables). Cost of feeds prepared or purchased for child will be calculated using UK food expenditure data.	☑				☑	☑	☑
Cost to families - equipment	Equipment (and cost incurred*) purchased specifically to prepare and store feeds (blender / mixer; hand blender; other food preparation equipment (e.g. chopping boards, cooking utensils); storage containers / bags; other)	☑						
Cost to NHS – formula feeds	Formula prescription (ml/day) (calculated using British National Formulary)	☑		☑				
Cost to NHS – dietary supplements	Supplement daily prescription (calculated using British National Formulary)	☑		☑				
Participant characteristics – demographics								
Child age	Date of birth	☑				☑		
Child sex	Male; female	☑				☑		
Child ethnicity	Census groups	☑				☑		
Parent ethnicity	Census groups	☑				☑		
Deprivation	Index of Multiple Deprivation (based on postcode)	☑				☑	☑	☑
Parental education	Highest level (census groups)	☑				☑		
Parental employment	Adapted from British Household Panel survey wave 18 employment question	☑				☑	☑	☑
Household composition	Number of dependent children (18 or under), marital status	☑				☑	☑	☑
Participant characteristics – clinical								
Child diagnoses	Name of each diagnosed condition	☑		☑		☑	☑	☑
Duration of gastrostomy	Date of gastrostomy insertion	☑		☑		☑		
Type of gastrostomy	Free text	☑		☑		☑	☑	☑
Tube diameter	Free text	☑		☑		☑	☑	☑
Reason for gastrostomy	Unable to meet nutritional requirements orally; Higher nutritional requirements - condition related; Food aversion; Unsafe swallow; Not known; Other	☑		☑		☑		

Variable	Proposed Measure	Source				Timings of data collection (months)		
		Parent	Child	Clinician	HES Data	0	12	18
Oral food proportion	No food or tastes; tastes only; regular oral food but most of nutrition via gastrostomy; regular oral food and less than 75% of nutrition via gastrostomy	☑				☑	☑	☑
Change in diet	Yes (previous diet: formula only, blended only, mix of formula / blended); No*	☑				☑	☑	☑
Feeding method	Bolus; Overnight; Combination of both	☑				☑	☑	☑
Equipment used to administer feeds	Pump; Syringe; Combination of both	☑				☑	☑	☑
NG tube prior to gastrostomy	Yes (date of insertion and removal); No	☑		☑		☑		
Fundoplication	Yes (date of procedure); No	☑		☑		☑	☑	☑

* Parent data will be requested for 12 month period before baseline, and between data points for follow-up (12 and 18 months). HES data will be requested for 24 months before baseline and for the 12 month follow-up to assess feasibility of long-term follow-up.

** We will assess the feasibility of using HES data for hospital treatment of tube blockages, tube malfunctions, stoma site infections, gastro-intestinal infections and pneumonia

*** Unit costs for healthcare interactions will be collected from published sources (for example, PSSRU Unit Costs of Health and Social Care) and applied to the relevant resource use. The costs of healthcare interactions will be calculated by the product of unit cost and resource use analyses.