LIFELAX – Diet and lifestyle vs. laxatives in the management of chronic constipation in older people

Protocol for a randomised controlled trial

1 Planned investigation

1.1 The research brief

The commissioning brief (HTA 01/10) specifies the key research question: "What is the comparative cost-effectiveness of laxatives compared with dietary and lifestyle changes in the treatment of elderly patients with chronic constipation". Dietary interventions are to be differentiated from bulk laxatives, such as bran, and dietary and/or lifestyle changes may be compared with single laxative agents.

1.2 The research questions addressed by this study

In studies of individual behaviour change strategies, particularly those relating to dietary change and exercise[1-3], personalised interventions have been shown to be more effective than standard, non-customised approaches. Elements of personalisation variously include: assessment of the importance of making a behaviour change and confidence in carrying out the new behaviour, where the individual is situated in the 'stages of change' model[4], motivational interviews[5]; discussion of current behaviour and of facilitators of and barriers to change; agreement of individualised goals and provision of personalised information and advice on behaviour change[2;6;7]; and follow-up reinforcement contacts[7]. Such personalised interventions, however, are typically more resource-intensive than non-individualised approaches[5]. For these reasons, it is important to ascertain not just the effectiveness but also the cost-effectiveness of these strategies.

We therefore propose a pragmatic three-armed trial to compare laxative treatment of chronic constipation in older people with both standardised, non-personalised dietary and lifestyle advice (delivered in a single, short consultation) and personalised dietary and lifestyle advice (delivered in a long consultation – or two shorter consultations, with telephone reinforcement). Through the trial we will address the following key questions, derived from the research brief:

- What is the comparative clinical and cost-effectiveness of laxatives versus a combination of dietary and lifestyle advice?
- What is the comparative clinical and cost-effectiveness of brief, standardised, non-personalised dietary and lifestyle advice versus personalised dietary and lifestyle advice, including reinforcement?

1.2.1 Objectives

1. To investigate the clinical and cost-effectiveness of laxatives versus dietary and lifestyle advice.
2. To investigate the clinical and cost-effectiveness of standardised versus personalised dietary and lifestyle advice.

1.3 Detailed plan of investigation

1.3.1 Trial design

The trial will take the form of a prospective, pragmatic[8], three-armed cluster randomised trial with an economic evaluation. Analysis will be on an 'intention to treat' basis. Participating practices will be randomised to one of three arms: (1) prescription of laxatives; (2) provision of standardised, non-personalised dietary and lifestyle advice; (3) provision of personalised dietary and lifestyle advice, with reinforcement.

A randomised controlled trial is the optimum design when evaluating behaviour change interventions. However, in this study, if the unit of randomisation was to be the individual patient, there would be a risk that health care professionals might provide elements of the dietary and lifestyle package to patients randomised to laxatives only. A solution to this problem is to 'cluster randomise' at the level of an entire practice, while collecting data about outcomes of care at the individual patient level. As patients within any one cluster are more likely to respond in a similar manner, such a design violates the assumption that the outcome for an individual patient is completely independent of that for any other patient. Therefore a cluster randomised design is not

as statistically efficient as a patient randomised design; it has lower statistical power than a patient-randomised trial of equivalent size[9] and sample sizes need to be inflated to compensate for this (1.3.6).

1.3.2 Setting

General practices in England and Scotland and the homes of older people (aged 50 years and over) from these practices.

1.3.3 Health technologies being assessed

1.3.3.1 Treatment strategies at the patient level

Study participants will be randomised to one of three treatment strategies (1.3.1).

Within the laxatives arm, free choice of class of laxatives will be allowed. There is at present insufficient evidence[10;11] of the relative superiority of one class of laxatives over another, or of combination therapies as opposed to single preparations. Free choice of laxative therapy will more closely replicate the situation which will pertain in routine clinical practice; adherence to treatment protocol is therefore expected to be better than where a change in drug is required. For similar reasons, leeway in dosage will be permitted, within dose ranges commonly used in clinical practice. To minimise the risk of prescribing sub-therapeutic doses, the intervention protocol will remind participating GPs of the therapeutic dose ranges for the available laxative preparations.

The dietary and lifestyle interventions will be informed by findings from previous trials of diet and lifestyle interventions[1;2;6;7]. They will also draw upon theories of individual behaviour change, including the concept of self-efficacy[12] and the stages of change model[4].

In both the standardised and personalised arms, the 'information package' will comprise practical, target-based advisory sheets on: diet – increased consumption of non-starch polysaccharides (NSP (fibre)) of both cereal and fruit and vegetable origin[13] and of bread and bran products[14]; hydration[15]; dentition[16]; mobility and exercise[17;18]; abdominal massage[18]; toilet habits[17]; what constitutes normal bowel function[19]; the action and potential side-effects of laxative use. Locality-specific information (e.g. details of local exercise programmes for older adults and of fruit-and-vegetable buying clubs) will be included in the package for those allocated to the personalised dietary and lifestyle intervention.

In both arms, this package will be delivered by practice or community nurses (according to local custom). Appointments will generally be offered at the surgery, though home visits will be an option where appropriate. In the standardised, non-personalised arm, there will be a single short (maximum of 10 minutes) appointment, with delivery of a standard pack of information and brief, general explanation of these information materials. In the personalised arm, there will be an initial long (30-45 minutes)[5] appointment (though this may be undertaken in two shorter appointment should clinic time so dictate) and the technique of 'motivational interviewing' – 'a directive client-centred counselling style for eliciting behaviour change by helping clients to explore and resolve ambivalence' [5] – will be employed. The personalised approach will include a patient-specific assessment of barriers to and facilitators of change and delivery of a personalised pack of information with individual targets. Patients in this arm will receive a follow-up motivational telephone call from the nurse at one week and one month after initial appointment.

A potential threat to patient recruitment and retention in this trial is patients' unwillingness to forego medication. For this reason, although diet and lifestyle will be the first-line treatment for patients allocated to those arms, the option of continuing laxative use (either prescribed or over-the-counter) will be available if required; the need for and use of such medication will be captured in patient diaries (1.3.5.1 and 1.3.5.3).

1.3.3.2 Training strategies for health professionals

An orientation and training programme will be developed for the practices recruited to the study. All practices will have an on-site training visit to discuss aspects of the treatment protocol and how it is to be delivered in the practice. In addition, a dietician with experience in health promotion will deliver in-practice training on how to deliver the dietary and lifestyle intervention to patients, as follows:

- Standardised dietary and lifestyle intervention – all primary health care professionals (general practitioners, practice and district nurses, health visitors) in the practice will be invited to a single, one hour session to introduce the programme and the patient pack.
- Personalised dietary and lifestyle intervention – all primary health care professionals (general practitioners, practice and district nurses, health visitors) in the practice will be invited to an initial one hour session to introduce the programme and the patient pack. Practice staff involved in delivering the intervention to patients will be invited to take part in two further 45 minute sessions on the delivery of a personalised pack and motivational interviewing techniques.

The choice of number and duration of training sessions is based on experience in other similar studies, and represents a balance between minimising the demands on busy health professionals' resources, whilst having sufficient time to motivate doctors and nurses and to equip them with the knowledge and skills required to deliver the interventions to patients. Our personal experience, reinforced by the literature[20], suggests that in-practice delivery of training of this nature is more cost-effective than delivery at a single, central location.

1.3.4 Target population

People aged 50 or over with chronic constipation living in private households. The choice of an age cut-off of people aged 50 or over has been made after due consideration of the morbidity statistics from general practice[21] which show that general-practitioner consultation rates for constipation take off in the 45-64 age group and rise steadily with age. The exclusion of residents in long-term care reflects the different morbidity and life-style experience of long-term care residents. We will focus on a predominantly ambulant population able to independently attend a primary care clinic.

1.3.4.1 Inclusion criteria

The complexity of the revised Rome criteria for functional constipation[22] militates against their use in screening for chronic constipation. Moreover, newly incident cases of constipation, especially amongst older adults, should be investigated to determine the underlying cause of the constipation and to eliminate more serious problems[23] before laxatives are prescribed.

This trial will therefore identify and recruit only 'prevalent' cases, defined in terms of those prescribed laxatives three or more times in the previous 12 months. Participants meeting this criterion will be identified from general practice computerised patient records using an electronic 'query' to interrogate repeat prescribing databases. It is recognised that the relapsing and remitting nature of constipation means that not all patients thus identified will be constipated (by objective or subjective criteria) at any given time. Eligible participants who have given informed consent will be invited to complete a baseline assessment during which current bowel function and perceptions of whether constipated will be elicited; these baseline data will be included as co-variates in our analysis (1.3.7).

1.3.4.2 Exclusion criteria

- Patients resident in long-term care.
- Patients with inflammatory bowel disease, intestinal obstruction/bowel strictures, known colonic carcinoma, and conditions contra-indicative to the prescription of laxative preparations[24].
- Inability to read and understand written treatment plans and educational material.
- Inability to complete outcome assessments, even with assistance (e.g. major cognitive impairment, lack of understanding of English).

1.3.5 Assessment of outcomes

1.3.5.1 Outcome measures

The primary outcome, and the criterion upon which the sample size calculations have been based, is patient-reported condition-specific quality of life at three months post recruitment (1.3.5.2). Our preferred measure of quality of life is the constipation-specific PAC-SYM / PAC-QOL[25], which has been demonstrated to have good validity and reliability. However, this measure is not utility-based. For the purposes of the economic evaluation (1.3.8), a measure of the utility placed by patients on

their health state will be required. The condition-specific measure of quality of life will therefore be supplemented by the generic, utility-based EQ-5D[26;27].

Secondary outcomes will include: bowel movement frequency; the presence/absence of the other Rome criteria for constipation; patients' own perceptions of whether or not they are constipated; patient satisfaction with bowel function; adverse effects of treatment; relapse / re-consultation rates; fluid and fibre intake (Table 1).

In addition, the cost implications of the condition and its treatment (e.g. GP consultations, purchase of prescribed and over-the-counter medication) will be assessed, as part of the economic evaluation (Table 2; section 1.3.8).

Table 1 Outcome measures

Primary outcome	**Measurement method**	**When**	**Where**
Health-related quality of life	Postal questionnaire	At three months post recruitment	Participant's home
Secondary outcomes	**Measurement method**	**When**	**Where**
Health-related quality of life	Postal questionnaire	At six and twelve months post recruitment	Participant's home
Number of bowel movements per week	Self-completed structured diary + Postal questionnaire	Daily for 6 months At 12 months	Participant's home
Other Rome criteria: straining at defecation, stool consistency, perceived incomplete evacuation	Self-completed structured diary + Postal questionnaire	Daily for 6 months & for 1 week at 12 months At 12 months	Participant's home
Subjective perception of whether constipated; satisfaction with bowel function	Telephone interview + Postal questionnaire	At 3 months At 6 months & 12 months	Participant's home
Adverse events: abdominal pain, nausea, bloating, flatulence, diarrhoea	Self-completed structured diary + Postal questionnaire	Daily for 6 months & for 1 week at 12 months At 12 months	Participant's home
Use of prescribed and OTC laxatives	Self-completed structured diary + Postal questionnaire	Daily for 6 months & for 1 week at 12 months At 12 months	Participant's home
Fluid and fibre intake	Self-completed structured diary + Postal questionnaire	1 day per month for 6 months At 12 months	Participant's home
Relapse rates: including repeat consultations	Self-completed structured diary; GP records	Daily for 6 months; Twelve months post recruitment	Participant's home (diary); General practices (GP records)
Personal measures of success with the management of constipation	Telephone interview	At 3 months and 6 months	Participant's home

Table 2 Measuring treatment impact

Impact	Measure	When	Where
Costs to participants of the condition and its management	Structured health diary; telephone interview; postal questionnaire	Using different methods, for six months	Participant's home
Consultation rates and laxative prescriptions	GP records	At twelve months post recruitment	General practices

1.3.5.2 Follow-up period

Maximum response to the interventions are expected within 12 weeks of initiation of treatment; this dictates that the primary outcome should be assessed at three months post recruitment. However, since a common criticism of behaviour change interventions is the lack of sustained effect, quality of life data will be collected again at six and twelve months post recruitment while symptom diaries will be completed daily for six months. Relapse rates (defined in terms of re-consultation and/or demand for further prescriptions for laxatives) will be monitored for twelve months post recruitment, through interrogation of patients' medical records. We believe that intensive follow-up of patients for six months coupled with extended monitoring of quality of life, consulting and prescribing data represents a reasonable compromise between placing excessive burden on respondents (posing threats to recruitment and retention rates) and assessing longer-term consequences of the interventions.

1.3.5.3 Methods of data collection

1.3.5.3.1 Base-line assessment (W^0)

Prior to any assessments being conducted, each participant will speak on the telephone with a member of the research team and be invited to discuss any aspect of participation in the study they wish. Once informed consent has been obtained the baseline assessment will be conducted. This assessment will include a short telephone structured interview and a short self completion questionnaire. Current bowel function (based on Rome criteria), fluid and fibre intake and patients' self-perceptions of whether they are currently constipated and levels of anxiety and depression[28] will be elicited and data on activities of daily living[29], condition-specific quality of life and laxative use (both prescribed and over the counter) will be collected. A weekly structured self-completed diary will be distributed and explained. The person conducting the baseline assessment will notify practices that patients are ready to begin the intervention (as per protocol) and practices will make an appointment to see participants to start the intervention. In following this approach we minimise the risk of patients who have not given informed consent receiving the intervention as the intervention will only be delivered once a signed copy of the consent form is sent to the practice with the instruction to begin the intervention. At this first appointment, treatment per intervention protocol (1.3.5.4) will be initiated. Should patients decide to withdraw when they return to collect either their laxative prescription or for their diet and lifestyle appointment, the practice will notify the research team and all baseline assessment data and patient identification data will be destroyed or deleted from the study database.

1.3.5.3.2 Health diary (daily for 6 months from W^0)

To minimise recall bias, data on bowel function (based on the Rome criteria)[22], fluid and fibre intake, perceptions of whether constipated and use of laxatives will be gathered by a structured (tick box format) health diary, completed each day and returned monthly for six months.

1.3.5.3.3 Follow-up self-completion questionnaires (W^{13} and W^{26} and W^{52})

Follow-up questionnaires, using up to two reminders, will be sent at W^{11} (for completion by W^{13}), W^{24} (for completion by W^{26}) and W^{50} (for completion by W^{52}). Data to be collected will be: condition-specific quality of life (1.3.5.1); Rome criteria[22]; and anxiety and depression[28].

Although structured interviews are the gold standard for collecting a large volume of complex data[30], the choice of postal questionnaires has been made to contain the cost of data collection. The use of postal questionnaires will also allow some blinding of outcome assessment (1.3.5.5).

Our recent experience in using postal questionnaires to gather information on quality of life and costs of treatment from ambulant, cognitively normal, older people with angina, in which we achieved response rates of 72%, 83% and 90% at baseline, 12-month and 24-month follow-up respectively, suggests that non-response bias will not be a significant problem.

1.3.5.3.4 Telephone interviews (W^{3-4}, W^{13} and W^{26})

Within two weeks of their consultation for diet and lifestyle advice a small sample of patients in the standardised and personalised intervention arms of the trial will receive a short postal questionnaire to ask about the diet and lifestyle advice they were given. The purpose being to monitor the content of the interventions. Short telephone interviews will be used to collect cost data on medication purchase (both prescribed and OTC), and other out of pocket expenses for the economic analysis. This interview will also ask patients about their personal levels of success in the management of their constipation. They will be conducted by a research secretary at W^{13} and W^{26} and data will be recorded directly onto a database by the interviewer. We are currently using this method effectively in a study of older people. Other resource use data will be collected from practice medical records (1.3.5.3.5).

1.3.5.3.5 Medical records (W^{52})

Data pertaining to consultation rates and prescription of laxatives for all study participants for the twelve months post recruitment will be abstracted from medical records. This will be done practice-by-practice at the end of the data collection period. Trained research nurses will interrogate paper-based and computerised records and will enter data directly to a database on lap-top computer. The electronic query used to identify patients at the beginning of the trial will be adapted to capture data on laxative prescriptions. We have used these methods of data collection to good effect in previous similar studies.

1.3.5.4 Participants' pathways through trial

		Activity
1		Potential participants identified from computerised practice databases using simple electronic query to flag individuals receiving prescriptions for constipation (3 or more in previous 12 months).
2		Initial screen by practice to identify clear exclusions.
3		Written invitation sent by practice (facilitated by research team) to patient to participate in study. Contact details form and pre-paid envelope included for patients wishing to join the study included. Research team to contact patient to answer questions and explain about process for informed consent. Consent form posted to patient with pre-paid envelope. Self completion questionnaire and pre-paid envelope also sent. Control patients will receive their diary (including pre-paid envelope) at this point.
4	W^0	When consent form is returned the telephone baseline interview will be conducted. patient advised to expect contact from practice to arrange 'intervention start' appointment.
5	W^1	Appointment at practice – laxative prescription issued or diet and lifestyle intervention initiated. All patient information and baseline data destroyed by research team if patient notifies practice of their wish to withdraw from study.
6	W^2	One week reinforcement phone call from nurse to patients randomised to personalised diet and lifestyle advice
7	W^{3-4}	Intervention fidelity measure – a small sample of patients in the standardised and personalised intervention arms of the trial will receive a short postal questionnaire to ask about the diet and lifestyle advice.
8	W^5	One month reinforcement phone call from nurse to patients randomised to personalised diet and lifestyle advice
9	W^{12}	Three month follow up outcome assessment (postal questionnaire) and collection of cost data and personal levels of success (telephone interview)
10	W^{26}	Six month follow up outcome assessment (postal questionnaire) and collection of cost data and personal levels of success (telephone interview)
11	W^{52}	Twelve month follow up outcome assessment (postal questionnaire & 1-week symptom diary). Review of practice notes to abstract data on consultation rates and prescription patterns.

1.3.5.5 Blinding of outcome assessment

Health technology assessment is essentially a pragmatic activity conducted in normal clinical practice. It follows that blinding doctors, nurses and patients to treatment is not desirable (even if practicable – which would not be the case here, since the three interventions are visibly and demonstrably different) since it distorts normal clinical practice. In contrast, blinding of assessors is desirable because it minimises subjective bias towards a given treatment. Where practical considerations (e.g. size of research team) preclude concealment of allocation of treatment from those collecting data, highly structured data collection instruments can reduce the risk of bias in data recording and analysis. In this study, complete concealment of the allocation is likely to be impractical. However, the individuals responsible for the delivery of training in the dietary and life-style intervention, and for the collection of qualitative data on facilitators of and barriers to adherence to treatment protocol, will not reveal their experiences in respect of individual practices to those collecting and analysing patient outcome data.

1.3.6 Sampling design and implementation

1.3.6.1 Practice recruitment and randomisation

General practices in England and Scotland will be invited by letter to participate. Standard sample size calculations for a cluster randomised trial[31] indicate that we will need to recruit 57 practices in total (1.3.6.3). This estimate is based on the number of patients likely to be available in the average-sized practice; if larger practices participate, the number of practices required may be slightly reduced. We will initially seek to include practices from local primary care research networks but may need to supplement with others, depending on take up. Practices agreeing to take part in the study will be randomised by computer to one of the three arms. We recognise that practices may have preferences with respect to allocation of interventions. We will make it very clear to the practices approached to participate in the LIFELAX study that allocation to intervention will be completely at random and that practice preferences cannot be taken into account. Randomisation will be carried out by an individual not otherwise involved in practice contact, or in data analysis.

1.3.6.2 Patient identification and recruitment

Two methods of patient identification were considered: incident and prevalent cases. Consultation rate data[21] indicate that there would be only a small number of incident cases per year in any one practice. Moreover, these incident cases would, at least initially, be subject to more intensive medical investigation[23], which would militate against inclusion in the trial. Finally, we are aware of experiences of differential rates of patient identification across active and control arms of previous cluster randomised trials (e.g. the UK BEAM trial) and the potential for selection bias that results from such differential rates. This risk is greater when incident cases are being identified, and when responsibility for identification lies with the clinician. For these reasons, only prevalent cases (1.3.4.1), which will be retrospectively identified through computerised records, will be considered.

The identification process will be through an independent interrogation of practice prescribing databases, and will therefore not be subject to influence by the participating clinicians. We believe that this approach will minimise selection bias.

To spread practice workload, patient recruitment in each practice will be spread over four months. It would not be practicable to identify all (i.e. across all 57 practices) potentially eligible patients prior to practice randomisation and patient contact. The reason for this is that bowel symptoms may fluctuate in patients and a patient identified as 'constipated' at a given point in time may no longer be 'constipated' several months later. We expect that the delivery of the intervention to practices will extend over 10 months. Initial eligibility of patients will be based on receipt of 3 or more prescriptions for laxatives in the preceding 12 months (1.3.4.1). If the patient identification query were to be run in all practices at the beginning of this 10 month period and patients thus identified were to be 'banked' until the intervention was delivered in a specific practice, some of those identified might no longer meet eligibility criteria, while others by then meeting eligibility criteria would not be considered for inclusion.

1.3.6.3 Sample size

Participating practices will be randomised to one of three arms. In calculating sample size for cluster randomised trials[31], it is necessary to take into account within-cluster variance, measured

by an intra-class correlation (ICC). Our experience in previous studies suggests that intra-class correlations of 0.05 for quality of life outcome are typical.

Preliminary analysis of data from the average-sized practices of one of the applicants suggests that there will be approximately 40 patients in such a practice meeting eligibilty criteria (1.3.4). We recognise that patients in practices allocated to the diet and lifestyle arms of the trial may be reluctant to undertake a change to their diet or lifestyle and may therefore withhold consent to participate. It is in anticipation of this risk that we have made the assumption that only 30 out of 40 patients identified will agree to participate and that only 25 will provide follow up data for 12 months.

Our primary outcome is a continuous variable – score on a quality of life (QoL) scale. In the absence of detailed data on the distribution of QoL scores in our population, we can nonetheless specify the effect size that we wish to detect. We arbitrarily set this at 0.3 standard deviations on the condition-specific quality of life scale. Within the literature on quality of life assessment, there is a growing consensus[32] that an effect size (i.e. change over time divided by standard deviation at baseline) of less than 0.2 represents a negligible change, an effect size of 0.2 up to 0.5 represents a 'small' effect, an effect size of 0.5 up to 0.8 represents a 'moderate' change and an effect size of in excess of 0.8 represents a 'large' change. These criterion values, which have been shown to be stable across a range of settings, have been established by reference to what clinicians and patients consider to be an 'important' difference – the emphasis is therefore on clinical rather than statistical significance. Our proposed effect size of 0.3 therefore represents the difference between the threshold values for 'small', 'moderate' and 'large' changes (0.5 – 0.2; 0.8 – 0.5).

It is important to note that the LIFELAX trial is not a comparison of an intervention with placebo or with normal practice. Instead, there are three active treatment groups. It is not unreasonable to assume that we might observe at least a small change over time in symptom-related and quality of life outcomes in all of these treatment groups. What we are primarily interested in is whether one intervention offers a relative advantage over the others. For example, if the changes over time for the laxative and standardised diet and lifestyle interventions were 'small' by the established criteria set out above, but a 'moderate' improvement was observed in the individualised diet and lifestyle arms, we might reasonably conclude that this intervention offered a relative advantage.

For an effect size of 0.3, 90% power, a significance level of 5%, an intra-class correlation of 0.04, and the ability to recruit and retain 25 patients per practice, we therefore need a total of 57 practices (19 per arm).

1.3.6.4 Strategies for improving compliance

The commitment of general practitioners and practice staff will be crucial to the success of the study. Educational events will be used to introduce the study protocol to health professionals from the participating practices. A regular newsletter to practices will report on progress in the study. Financial support will be provided to practices to identify and recruit patients. CPD accreditation will be sought for in-practice training. An educational meeting (again accredited) for participating practices will be held at the end of the study to disseminate findings and recommended strategies.

We believe that the availability of "rescue" medication for patients randomised to the diet and lifestyle arms will reduce the risk of non-consent or loss to follow-up, due to anxieties about not being able to use medication.

1.3.7 Statistical analysis

Analysis will be on an intention-to-treat basis. No sub-group analyses are planned. The data will be analysed using mixed effects models, accepted practice for the analysis of data from cluster randomised trials[31]. Variation between practices and variation between patients nested within practices will be fitted as random effects. The difference between treatment strategies (i.e. the three arms of the trial will be fitted as fixed effects. Most of the outcome variables (e.g. quality of life scores, number of days with (or without) symptoms are continuous and will be analysed assuming a Normal error structure. The dependent variable in each model will be point of follow-up (three, six and twelve months outcomes for quality of life, symptoms and perceptions of bowel function; twelve months for consultation and prescription rates). For each patient, baseline data will be included as a co-variate. The mixed models will be used to generate interval estimates for the differences between alternative treatment strategies.

1.3.8 Economic evaluation

1.3.8.1 Perspective of the evaluation

We will conduct a cost-effectiveness analysis, placing particular emphasis on the subset of costs and effects relevant to address the health service perspective at a macro level. We will supplement this by an individual participant perspective. Our selected outcome measures include condition- and treatment-specific quality of life and a generic utility-based measure of health state, measured at the individual level. We will also record the costs of the condition and its management which are met directly by the patients themselves.

1.3.8.2 Measure of benefits used and type of study

Considering all the measures of effectiveness estimated within the clinical trial, a cost-consequence analysis[33] will be outlined alongside the cost-effectiveness analysis. In the cost-consequence analysis, clinical and QoL profile scores, resources used for the implementation of the intervention strategies and related costs will be presented in a disaggregated way. For each arm of the trial, the breakdown of costs and outcomes will be listed in a tabular format; no summary measures will be presented. This type of evaluation and presentation provides readers with a more transparent interpretation of the results and allows them to make a more selective application of the findings to specific decision-making contexts.

Although quality of life is an important indicator of benefit in the treatment of constipation, and is the primary outcome measure in this study, none of the currently available condition-specific measures yield a unique QoL score. A comparison/synthesis of costs and outcomes based on each of the separate QoL dimensions in our chosen profile measures would be methodologically invalid. For this reason, a utility-based, index measure – the EQ-5D[26;27] – will also be used, to facilitate calculation of Quality Adjusted Life Years (QALYs). We are, however, aware of the concerns about the use of QALYs in devising resource allocation strategies between different age cohorts. Therefore, we aim to develop or apply already existing 'corrective' measures to the results we will obtain, so that our findings will not have unfavourable implications for the funding of health technologies for older people.

Furthermore, we anticipate that the EQ-5D may not be sensitive enough to detect differences in the population being studied. Therefore, alongside this utility-based measure, we will calculate discomfort-free days (DFDs) as a new measure of outcome. This measure will include the impact on patients' wellbeing of unwanted symptoms due to both constipation and treatment side-effects. It will be a crude but meaningful measure of the patients' perceived effectiveness of treatment. DFDs will be derived through the self-completed structured diaries, in which patients will be asked to report the overall impact of both the symptoms of constipation and side-effects of the laxatives on their wellbeing. Severity of impact will be graded in levels, and the number of days spent in each level of discomfort will be calculated. This information will be used to assess correlation with DFDs responses. We believe that the comparison of DFDs with EQ-5D utilities will represent a useful addition to the body of knowledge on the assessment of cost-effectiveness in trials where the main impact is expected to be on palliation of symptoms and improvement of the quality of life, rather than on extension of life.

1.3.8.3 Resources data collected within the trial and costing methods

Costs to the National Health Service (NHS) will be estimated on the basis of the use of resources needed to implement the three proposed treatment strategies as well as those related to the subsequent use of services. Relevant costs include prescribed laxatives, consultations with GPs and nurses, and services related to the dietary and lifestyle interventions, such as the delivery of advice packages. The costs of preparing and delivering information materials and of training health care professionals in their use will also be estimated. These latter represent 'start-up' sunk costs, which would not be recurrent once the intervention is in place. Allowance against future savings will be made in the cost-effectiveness analysis for this initial investment.

Data on consultation rates and drugs prescribed will be collected through extraction of data from medical records of trial participants. Use of resources related to case management services and start-up costs will be gathered from the protocol, which will describe in detail how the dietary and lifestyle intervention will be delivered. Costs related to the use of medication and health services will be assigned using national published data for the United Kingdom[24;34].

Costs falling on the NHS will be supplemented with costs falling on patients themselves. These will be derived through telephone interviews, and will include information about the patients' purchase of over-the-counter laxatives and any other possible expenditure relating to the management of constipation (e.g. use of complementary medicine, travel costs). Where possible, participants will be asked to report costs and quantities separately.

1.3.8.4 Synthesis of costs and outcomes

If there is not statistically and clinically significant evidence that one treatment strategy is superior to another in terms of health utilities or DFDs, a cost-minimisation framework will be used and the adoption of the less expensive strategies will be recommended. Similarly, recommendations for adoption will be made if one strategy appears to be more effective and less costly than its comparator(s). If one strategy appears to be more effective but more expensive than its comparator(s), estimates of incremental cost-effectiveness ratios will be generated and compared. A judgement will be required in a policy-making context to establish whether the additional benefits warrant the additional costs. In any case, results will be presented taking into account the issues of the generalisability of the results to other local settings.

1.3.8.5 Sensitivity analysis

Issues of uncertainty in assumptions, methods and data, and of the generalisability of the results will be addressed in the sensitivity analysis, where the robustness of the results to any variations in key data inputs to the study will be tested. Moreover, a sensitivity analysis, taking into account of differences in resource use which are practically significant (i.e. potentially costly) but which have not been shown to be statistically significant, will be also be undertaken.

1.3.9 Ethical arrangements

Approval for this study will be sought from Scotland A Multicentre Reseach Ethics Committee (MREC) and subsequently from the relevant Local Research Ethics Committees. We will follow the recommendations of the MREC (the Medical Research Council and Consumers for Ethics in Research (CERES) in conducting this trial and in providing participants with appropriate information.

The risks to patients are anticipated to be minimal (particularly since the option of rescue medication is available to those allocated to the diet and lifestyle arms). Conversely, there are potential benefits in terms of symptom relief and enhanced quality of life for all participants (since all groups get an 'active' intervention and are not denied treatment). Written information leaflets will be used to inform those invited to participate about the potential benefits, risks and implications of participation, and this written information will be reinforced by the nurse when patients are invited to participate. Those invited to participate will have a minimum of a week to consider whether they wish to join the study. Affirmation of consent (for participation in the trial and for access to medical records) will be requested at the follow-up consultation (1.3.5.4) and baseline data from those withholding consent will be destroyed. We do not anticipate that anyone eligible for the study would be incapable of giving fully informed consent. The University of Newcastle recommends that original research data be retained for a minimum of ten years and we will follow this recommendation. All data will be held in compliance with the requirements of the Data Protection Act.

Hutton[35] has suggested that cluster randomised trials pose unique ethical issues. In particular, since randomisation in this trial is at the level of the practice, patient consent must essentially be post-randomisation. As stated above, we believe that the offer of rescue medication to patients in practices allocated to the diet and lifestyle arms will go some way to ameliorating this constraint on patient choice.

2 Reference List

Reference List

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