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LIFELAX – diet and LIFEstyle versus LAXatives in the management of chronic constipation in older people: randomised controlled trial

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The research reported in this issue of the journal was commissioned by the HTA programme as project number 01/10/04. The contractual start date was in June 2003. The draft report began editorial review in October 2009 and was accepted for publication in February 2010. As the funder, by devising a commissioning brief, the HTA programme specified the research question and study design. The authors have been wholly responsible for all data collection, analysis and interpretation, and for writing up their work. The HTA editors and publisher have tried to ensure the accuracy of the authors' report and would like to thank the referees for their constructive comments on the draft document. However, they do not accept liability for damages or losses arising from material published in this report.

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Abstract

LIFELAX – diet and LIFEstyle versus LAXatives in the management of chronic constipation in older people: randomised controlled trial

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Objectives: To investigate the clinical effectiveness and cost-effectiveness of laxatives versus dietary and lifestyle advice, and standardised versus personalised dietary and lifestyle advice.
Design: A prospective, pragmatic, three-armed cluster randomised trial with an economic evaluation.
Setting: General practices in England and Scotland, UK.
Participants: People aged ≥ 55 years with chronic constipation, living in private households. Participants were identified as those who had been prescribed laxatives three or more times in the previous 12 months, or with a recorded diagnosis of chronic functional constipation.
Interventions: Prescription of laxatives, with class of laxative and dose at the discretion of the GP and patient (standard care control arm); standardised, non-personalised dietary and lifestyle advice; and, personalised dietary and lifestyle advice, with reinforcement.
Outcome measures: The primary outcome was the constipation-specific Patient Assessment of Constipation-Symptoms (PAC-SYM)/Patient Assessment of Constipation-Quality of Life (PAC-QOL).
Results: The trial planned to recruit and retain 1425 patients from 57 practices (19 per arm); however, only 154 patients were recruited from 19 practices. Due to these low recruitment rates it was not possible to report the conventional trial findings. Baseline characteristics of the sample from data gathered from both postal self-completion questionnaires and face-to-face interviews suggest that our sample experienced very few symptoms of constipation (PAC-SYM) and that the condition itself did not have a major impact upon their quality of life (PAC-QOL). The low level of symptoms of constipation is most likely explained by 90% of the sample using a laxative in the previous week. Most participants in our sample were satisfied with the performance of their laxatives, and levels of anxiety and depression were low. Their fibre consumption was classified as 'moderate' but their average water consumption fell below the recommended guidelines. Daily diaries, completed each day for a period of 6 months, were analysed primarily in terms of overall response rate and item response rates, and the participants accepted this method of data collection. For the economic evaluation, all of the trial arms experienced a reduction in utility, as measured by EQ-5D. There was no statistical evidence to suggest that either the personalised intervention arm or the standardised intervention arm was associated with significant changes in utility at 3 months compared with the control arm. Data on related health-care costs show a cost saving of £13.34 for those in the personalised arm, compared with the control arm, and a smaller cost saving for the standardised arm. These savings

primarily occurred because of reduced hospital costs. There was no significant change measured in utility, so the personalised arm appeared to be the preferred course, producing the greatest cost savings.
Conclusions: Due to the low number of participants in the trial, no firm conclusions could be drawn about the effectiveness of the interventions. However, a number of factors that contributed to the conduct and progress of the trial are highlighted, which may be relevant to others conducting research on a similar topic or population.
Trial registration: ISRCTN73881345.
Funding: This project was funded by the NIHR Health Technology Assessment programme and will be published in full in *Health Technology Assessment*; Vol. 14, No. 52. See the HTA programme website for further project information.

Contents

List of abbreviations

BCC	behaviour change counselling
BNF	*British National Formulary*
CI	chief investigator
CONSORT	consolidated standards of reporting trials
COREC	Central Office of Research Ethics Committees
CRB	Criminal Records Bureau
CTA	Clinical Trial Authorisation
ctIMP	clinical trial of an investigational medicinal product
DDX	Doctors' and Dentists' Exemption (certificate)
DFD	discomfort-free day
DH	Department of Health
DINE	Dietary Instrument for Nutrition Education
EQ-5D	European Quality of Life-5 Dimensions
GI	gastrointestinal
GMC	General Medical Council
GMS	General Medical Services
GP	general practitioner
HADS	Hospital Anxiety and Depression Scale
HRQoL	health-related quality of life
HTA	Health Technology Assessment (programme)
ICC	intraclass correlation
LIFELAX	diet and LIFEstyle versus LAXatives in the management of chronic constipation in older people
LREC	Local Research Ethics Committee
MHRA	Medicines and Healthcare products Regulatory Agency
MREC	Multi-Centre Research Ethics Committee
NDNS	National Diet and Nutrition Survey
NIHR CRN	National Institute of Health Research Clinical Research Network
NLI	no local investigator
NoReN	Northern Primary Care Research Network
NPM	Normalisation Process Model
NRES	National Research Ethics Service
NSP	non-starch polysaccharide
NYReN	Northern and Yorkshire Primary Care Research Network
OTC	over the counter (medication)
PAC-QOL	Patient Assessment of Constipation-Quality of Life

continued

PAC-SYM	Patient Assessment of Constipation-Symptoms
PCRN	Primary Care Research Network
PCT	Primary Care Trust
PI	principal investigator
PIL	patient information leaflet
PIS	patient information sheet
QALY	quality-adjusted life-year
QOF	Quality Outcomes Framework
QoL	quality of life
R&D	research and development
RCT	randomised controlled trial
REC	Research Ethics Committee
RM&G	Research Management and Governance
SCFAs	short-chain fatty acids
SfS	Support for Science (funding)
SPCRN	Scottish Primary Care Research Network
SPPIRe	Scottish Practices and Professionals Involved in Research
SSA	site-specific assessment
SSI	site-specific information
STEPS	Strategies for Trial Enrolment and Participation Study
STOOL	Stepped Treatment Of Older adults on Laxatives
TSC	Trial Steering Committee
USP	unique selling point

All abbreviations that have been used in this report are listed here unless the abbreviation is well known (e.g. NHS), or it has been used only once, or it is a non-standard abbreviation used only in figures/tables/appendices, in which case the abbreviation is defined in the figure legend or in the notes at the end of the table.

Preface

In 2001, the Health Technology Assessment (HTA) programme produced the commissioning brief (HTA 01/10/04) for a trial on the use of a diet and lifestyle intervention versus laxatives to manage chronic constipation in older adults. The commissioning brief specified 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?' The brief was based on recommendations of a HTA-commissioned systematic review, which had found only weak evidence that laxatives can improve stool frequency and consistency, and related symptoms. Dietary and lifestyle interventions (increase in consumption of dietary fibre and fluid, moderate exercise, obeying the call to stool) had been shown to alleviate constipation. More generally, in studies aimed at the modification of dietary behaviour, brief interventions had been shown to have limited effect, while intensive, patient-tailored interventions had been more effective, though costly.

In response to the commissioning brief, the research team designed a pragmatic three-armed trial [diet and LIFEstyle versus LAXatives in the management of chronic constipation in older people (LIFELAX) – International Standard Randomised Controlled Trial Number (ISRCTN)73881345] 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, with telephone reinforcement). Through this study design the trial team was able to address the following key questions, derived from the research brief:

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

Running simultaneously with LIFELAX was another HTA-commissioned complex randomised controlled trial (RCT) investigating the cost-effectiveness of the stepped treatment of older adults on laxatives [Stepped Treatment Of Older adults on Laxatives (STOOL) – ISRCTN11557289]. The HTA Commissioning Board funded a small qualitative study alongside the STOOL and LIFELAX trials to investigate the definition and meaning of constipation among older people and health professionals. The results of this pilot work were used to inform a number of decisions made by the LIFELAX trial team while developing the interventions, the data collection tools and preparing patient information sheets.

Set-up and preparation for the LIFELAX trial (the development of the interventions, data collection tools – questionnaire and diaries, the production of the trial protocols, the production of practice training resources, and applications for regulatory, ethics and research governance approval) started in June 2003. Major changes to the Ethics and Research Governance structure and process during the life of the trial, challenges in practice recruitment and the lower than anticipated levels of patients' participation meant that recruitment targets were not met in the time agreed with the HTA. Towards the end of the recruitment period available to LIFELAX, the infrastructure to support research activities in the primary care setting was in place [initiatives such as the UK Primary Care Research Networks (PCRNs), the UK Local Comprehensive Research Networks]. However, these networks were still very much in their infancy, and the LIFELAX Trial Steering Committee made the decision in September 2007 to close recruitment and follow up the small number of participants in the trial rather than recommend approaching the HTA for a further extension.

In conjunction with LIFELAX, the HTA programme funded an integrated qualitative process evaluation study. The aim of the process evaluation was to develop a critical understanding of the social processes and practices implicated in the development, implementation and dissemination of a RCT within the field of HTA.

Because the process evaluation was ethnographic, qualitative research techniques were used, and it was therefore not appropriate to set out research questions in hypothetical form.

Methodologically, the approach taken by the process evaluation was a shift away from the conventional, with the relationship between the quantitative (LIFELAX) and qualitative (process evaluation) being *integral* rather than *complementary*. In this respect the process evaluation was concerned primarily with documenting HTA *in action* through implementation of an RCT, rather than the provision of supplementary qualitative data to support the key LIFELAX outcome measures.

Due to the lower than necessary levels of patient recruitment it has not been possible to conduct a full evaluation of the interventions, therefore this report has a slightly different emphasis to the model HTA monograph. We describe the background to, and rationale for, the study. We describe the development of the interventions and the various training resources. We present the design of the trial and detail the various strategies and techniques used in its implementation to optimise practice and patient participation. We examine the various barriers to successful implementation of LIFELAX at a practical level. We present the findings of the process evaluation and discuss the contribution it makes to our understanding of a complex intervention at work using the Normalisation Process Theory and the implications for future complex interventions in primary care.

Executive summary

Background

The management of constipation in the over-55s is costly, generating far in excess of 450,000 general practitioner (GP) consultations per year in the UK, at an estimated cost of more than £4.5M per year. In older adults living in the community, approximately 20–25% have symptoms of constipation. The propensity to consult increases with age – for a GP with an average list size of 2000, approximately 16 patients aged 55 and over will consult about constipation each year (McCormick A, Fleming DF, Charlton J. *Morbidity statistics from general practice: fourth national study*. OPCS: London; 1995).

Though often trivialised as a medical problem, for people with chronic constipation the impact on quality of life (QoL) is considerable and the burden on health-care resources is substantial.

Objectives

To investigate the clinical effectiveness and cost-effectiveness of:

1. laxatives versus dietary and lifestyle advice
2. standardised versus personalised dietary and lifestyle advice.

Methods

Design

A prospective, pragmatic, three-armed cluster randomised trial with an economic evaluation.

Health technologies being assessed

1. Prescription of laxatives, with class of laxative and dose at the discretion of the GP and patient (standard care control arm).
2. Standardised, non-personalised dietary and lifestyle advice.
3. Personalised dietary and lifestyle advice, with reinforcement.

Setting

General practices in England and Scotland, UK.

Participants

People aged ≥ 55 years (lowered to 50 years during the course of the trial) with chronic constipation, living in private households. Participants were identified as those who had been prescribed laxatives three or more times in the previous 12 months, or with a recorded diagnosis of chronic functional constipation.

Outcome measures

The primary outcome was the constipation-specific Patient Assessment of Constipation-Symptoms (PAC-SYM)/Patient Assessment of Constipation-Quality of Life (PAC-QOL). Secondary outcomes comprised: European Quality of Life-5 Dimensions (EQ-5D), reported number of bowel movements per week; the presence/absence of the other Rome II criteria for constipation; and adverse effects of treatment; and relapse rates.

Intervention development

The content and mode of delivery of the two intervention arms was developed by working closely with patients and practice staff from two GP practices. The patient information underwent a series of revisions following extensive patient feedback using a range of cognitive interview techniques.

Results

Baseline data

The trial planned to recruit and retain 1425 patients from 57 practices (19 per arm); ultimately, 154 patients were recruited from 19 practices. Due to the low recruitment rates, we are not able to report the conventional trial findings. We report the baseline characteristics of our sample from data gathered from both the postal self-completion questionnaire and the face-to-face interview. These data suggest that our sample experienced very

few symptoms of constipation (PAC-SYM – Frank L, *et al*. Psychometric validation of a constipation symptom assessment questionnaire. *Scand J Gastroenterol* 1999;**34**:870–7) and the condition itself does not have a major impact upon their QoL (PAC-QOL – Marquis P, *et al.* Development and validation of patient assessment of constipation quality of life questionnaire. *Scand J Gastroenterol* 2005;**40**:540–51). The low level of symptoms of constipation is most likely explained by the fact that 90% of the sample had used a laxative in the previous week and thus were asymptomatic for constipation. Most people in our sample were satisfied with their laxatives in terms of the time they took to work and the effect they had on their stools. Levels of anxiety and depression were low in this group.

Fibre consumption can be classified as 'moderate' (Roe L, *et al*. Dietary intervention in primary care: validity of the DINE method for diet assessment. *Fam Pract* 1994;**11**:375–81). There was therefore scope for an intervention that focused on increasing dietary fibre to be effective. Characteristically in a sample of this age, average water consumption fell below the recommended guidelines**.**

Diary data

The daily diaries were analysed primarily in terms of overall response rate and item response rates. The diary was completed each day for a period of 6 months. The results show that the daily diary developed for the diet and LIFEstyle versus LAXatives in the management of chronic constipation in older people (LIFELAX) trial was an acceptable method of data collection for participants.

Economic data

With regard to the economic evaluation, all of the trial arms experienced a reduction in utility, as measured by EQ-5D. There was no statistical evidence to suggest that either the personalised intervention arm or the standardised intervention arm was associated with significant changes in utility at 3 months compared with the control arm. Data on related health-care costs show a cost saving of £13.34 for those in the personalised arm, compared with the control arm, and a smaller cost saving for the standardised arm. These savings primarily occurred because of reduced hospital costs, offset by a smaller increase in costs incurred through additional telephone consultations. As there was no significant change measured in utility, cost minimisation would suggest that the personalised arm would be the preferred course, as it produced the greatest cost savings. This finding is qualified by the fact that the statistically significant reduction in health-care costs was due to a relative small number of cases in this relatively small sample; confidence limits around all estimates are large.

Integrated qualitative process evaluation

Background

The randomised controlled trial (RCT) is the primary means by which clinically reliable knowledge and 'evidence' is constructed within the field of health technology assessment (HTA). The importance of the RCT lies not simply in its apparent methodological security, but in the social and political uses to which its results might be put. Evidence is a vital element of the politics of health care at the beginning of the twenty-first century: its production and application are politically contested both within the NHS and by specific interest groups, ranging from political parties to advocacy groups for particular groups of service users. Given the importance of the RCT in contemporary health care it is surprising that this crucial means of the social organisation and production of knowledge about health care has not been subject to sustained empirical attention in depth – but has instead been mainly the focus of macro-level analyses, such as that by Faulkner (Faulkner A. Strange bedfellows' in the laboratory of the NHS? An analysis of the new science of health technology assessment in the United Kingdom. In Elston MA, editor. *The sociology of medical science and technology*. Oxford: Blackwell; 1997. pp. 183–207). The process evaluation embedded within the LIFELAX RCT contributed toward addressing this gap, through the application of ethnographic research techniques to the empirical investigation of the social organisation, production, and effects, of the RCT in practice.

Objectives

The process evaluation addressed the following specific questions:

1. *Formation* How are ideas about the appropriateness of health technologies and their clinical applications formed and

mobilised in practice; and how are the interests of consumers and other users defined and incorporated in the organisation of the trial?
2. *Integration* How are specific clinical and methodological problems within an RCT identified and resolved within professional groups and networks; how is the trial integrated into the existing organisation of clinical service provision, and what professional and organisational dynamics are involved in this integration; and how is participation in the RCT negotiated and understood by subjects?
3. *Implementation* How is the production of results negotiated and organised within networks of researchers; how are its results mediated to the wider community and how is this negotiated and organised, both formally (through report writing and presentation); and, informally, how are the mechanisms and results of the trial understood by subjects?
4. *What lessons can be learned that will improve the organisation and conduct of HTA RCTs in the UK – and further afield?* This study has important implications for the organisation and conduct of HTA. It is important that its results can inform and develop both policy and practice.

Methods

Study group

Purposive sampling from three specific groups of participants in the trial: (1) project management and steering group ($n = 11$); (2) general practitioners (GPs), practice managers ($n = 6$) and nurses ($n = 9$) working to recruit and deliver patients to the trial and conduct the interventions; and (3) patients ($n = 23$) participating in the trial.

Data collection and analysis

A combination of qualitative research techniques were used, broadly following the precepts of Glaser and Strauss' (1967) model of constant comparison to develop first order analyses of the data. Throughout the contact period with each group a programme of semistructured interviews was undertaken. Some members of the trial team were interviewed iteratively across the life of the trial as new issues arose. All semistructured interviews were audio-taped with the respondent's consent, and transcripts formed the data subjected to formal analysis. The constant comparative method of qualitative analysis was carried out. Emerging themes were applied to the Normalisation Process Model (NPM) (May C. A rational model for assessing and evaluating complex interventions in health care. *BMC Health Serv Res* 2006;**6**:86).

Fieldwork commenced with initial mapping of the technical and social components of the trial. This mapping identified both the stakeholders and key structures of the system, from which a sample of both intervention situations and interviewees were chosen. Where observation was possible (e.g. at meetings or presentations), it involved the production of contemporaneous field notes from which analytic themes and categories were identified. It was important to observe routine and problematic applications of the trial, such as negotiations regarding the implementation of the protocol in busy primary care practices. Local documentary materials (e.g. protocols, correspondence, minutes of meetings, notices, leaflets, entries in newsletters) in which the trial was explained to professionals and subjects were analysed for comparison with themes emergent in the interview data, and with the wider literature concerning the particular form of intervention, and with HTA as a discrete field.

Results

The trial team followed the guidelines set out by the Research Management and Governance framework (RM&G – Central Services Agency, 2008) for clinical trials in the UK. However, certain milestones proved difficult to attain. In particular, the experience of the trial team was that RM&G guidelines were subject to localised, and sometimes inflexible, interpretation by governance bodies implicated in the research, whereas the Multi-Centre Research Ethics Committee (MREC) stipulations were also difficult to negotiate in practice. As an example, observation of the trial team revealed that they had significant difficulty in implementing the multicentre RCT when a shared understanding of what constituted 'risk to patients' was lacking across sites. A great deal of the trial team's resources were therefore spent in developing creative and workable solutions to emerging practical problems of implementation. As demonstrated by a growing number of reports in the literature (e.g. Wald DS. Bureaucracy of ethics applications. *BMJ* 2004;**329**:282–4), the LIFELAX trial was not alone in experiencing these difficulties.

The LIFELAX trial depended on cooperation between the trial team and key individuals from a number of external organisations. To facilitate administrative work, the trial manager actively identified key contacts and developed working relationships with them through a sequence of telephone calls and/or written communication. In this regard the trial relied heavily upon the 'social

aptitude' of the trial manager and his tactful approach in requesting additional resources. Social skills are infrequently identified as a key component of a trial manager's repertoire, yet they proved to be pivotal in the development of the LIFELAX trial, despite its early closure.

In following the research brief to assess the cost-effectiveness of diet and lifestyle interventions for the treatment of chronic constipation, the trial team developed nurse training packages based on Behaviour Change Counselling (BCC) techniques. Despite the time, expertise and financial resources spent on these interventions, the feedback from the interviewed primary care staff was that chronic constipation was a comparatively low priority issue for general practices. The perspective of practice staff can be summarised in three key points:

1. Chronic constipation was regarded as being successfully managed via laxatives.
2. Patients with chronic constipation typically saw their GP or a community nurse, therefore the practice nurses viewed the issue of constipation management as falling outside their remit of work
3. Some practice nurses described the BCC approaches as part of their current skill set, and therefore reported that the training interventions had little practical benefit for their routine patterns of work.

In this respect, the trial was perceived by some staff as giving nurses additional work, for a condition of low priority, and offering an intervention that, at best, was seen as relatively elementary to professional nursing practice. The participants interviewed through the process evaluation struggled to articulate whether they had benefitted from taking part in the research, while most of those attending practices randomised to the BCC arm did not view their consultation as differing from a routine nurse-led interaction.

Recommendations for research

A number of issues regarding the development and implementation of RCTs have been identified through the conduct of the process evaluation. The problem of the trial's topic, setting and training packages may have been identified had a prior feasibility study been conducted. At the time of the LIFELAX trial the HTA programme did not fund pilot studies of this nature, although the HTA have now changed their policy in this regard. However, numerous system-wide problems – such as the changing RM&G guidelines and research briefs that did not match General Medical Services contracts – also taxed the capacity of the trial to be successful. Following the results of the process evaluation, and the input of several of the reviewers of this report, we suggest the following:

1. Improved means and methods of communication are required between governance bodies, MRECs and researchers regarding the best way to conduct RCTs that are ethically, methodologically and practically sound.
2. There is a need for a clear and consistent means of applying for RM&G approval across Primary Care Trusts.
3. There is a clear need for pilot studies prior to the design and implementation of HTA RCTs:
   i. Pilot studies should assess the feasibility of all aspects of the intended research but, specifically, ensure that the assumptions underpinning the study are correct. These assumptions may be multiple but should ensure that: (1) there is an identified need for a technological intervention; (2) the intended beneficiaries also perceive a need for intervention and are in equipoise between the proposed interventions and control; and (3) the definition of the need or problem is commensurate between researchers, users and beneficiaries.
   ii. Pilot studies should assess whether the interventions will enable the intended users and/or beneficiaries to achieve relevant goals (such as *disposal* of symptoms).
   iii. Pilot studies should assess whether the intended interventions fit within existing patterns of work, and where they do not, assess the likely disruption and acceptability to intended users.
   iv. Pilot studies designed to assess the feasibility of the research should be conducted prior to any significant investment in the development of an RCT.

Trial registration

This trial is registered as ISRCTN73881345.

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The National Institute for Health Research Health Technology Assessment programme.

Chapter 1
Background

Introduction

As a medical problem, constipation is often trivialised.[1] However, chronic constipation has a considerable impact upon the individual and all of the health-care resources associated with managing the condition. The effect of chronic constipation on quality of life (QoL) is considerable,[2,3] and the burden on health-care resources, in terms of visits to health-care practitioners, and medications, is substantial.[4] In England and Wales, constipation generated some 450,000 general practitioner (GP) consultations per year in 1991–2,[5] at an estimated cost of £4.5M per year.[6] The net ingredient cost in 2005 of prescriptions for laxatives was approximately £50M per year in England alone.[7]

Defining constipation and 'normal' bowels

Constipation is 'variably defined'[8] by patients and medical professionals and is a common complaint of industrialised societies.[9] Patients perceive 'regularity' to be an important variable in determining good health.[10] In *Scouting for Boys*,[11] Baden Powell declared that in order 'to make yourself strong and healthy it is necessary to begin with your inside', and recommendations for this included 'making the stomach work to feed the blood' with exercises such as the 'cone', or 'body bending', and 'twisting'. In order to 'make the bowels active to remove the remains of food and dirt from the body' he suggested 'body bending' and 'kneading the abdomen', and suggested his scouts 'drink plenty of good water' and had, what he referred to as, a 'regular daily rear'.

The frequency and consistency of stools are important in defining constipation and 'normal bowels', both in lay and clinical definitions. Regarding 'frequency', clinicians consider passing a stool anywhere from three times a day to three times a week as being 'normal bowel function'.[12] Regarding 'consistency', as this is linked to transit time through the gut it is considered by clinicians to be a useful indicator of normal bowel function.[13–15] In everyday life, however, constipation means different things to different people.[16,17] Even to health-care professionals constipation remains a largely subjective diagnosis.[18] As the experiences of the STOOL (Stepped Treatment Of Older adults on Laxatives) trial and its associated qualitative study show, both constipation and normal bowel function are so difficult to define that it is entirely understandable that there is often a mismatch between what patients and health-care professionals mean when they use the term 'constipation' (p. 67).[19]

Clinical definitions

It is not surprising that constipation is subjectively diagnosed when one considers the lack of an accepted definition of constipation in clinical practice. Attempts to define it have been made and the following working definition has been proposed:[18] 'straining at passing stools for more than 25% of bowel movements'. Others attempts at a definition have used the frequency of bowel movements: passing a stool 'less than three times per week' has been offered as an operational definition of constipation in clinical and epidemiological research.[20,21] According to the Rome II criteria for functional constipation,[22] the 'gold standard' criteria at the time of designing the LIFELAX (diet and LIFEstyle versus LAXatives in the management of chronic constipation in older people) trial, for a diagnosis of constipation, individuals are required to have two or more of the following symptoms present for at least 12 consecutive weeks in the previous 12 months:

- straining in more than one in four defecations
- lumpy or hard stools in more than one in four defecations
- sensation of incomplete evacuation in more than one in four defecations
- manual procedures (e.g. digital evacuation or support of the pelvic floor) in more than one in four defecations
- fewer than three defecations per week.

In the more recent Rome III criteria, a less restrictive time frame is introduced. Symptoms must have begun 6 months prior to diagnosis and be active for 3 months. Thus, onset of symptoms

should begin at least 6 months before clinical presentation and the diagnostic criteria must be fulfilled for the last 3 months (rather than 1 year for Rome II).[23]

Considering the complexity of the above, it is entirely understandable that there is so little agreement between a patient's self-perceived constipation and assessments based on the Rome II criteria.[14,19] With the Rome II criteria for constipation being so far removed from the patient definition,[19] underestimation of the prevalence of condition could be expected. In a systematic review of studies of the epidemiology of constipation in North America,[24] the authors reported that the prevalence of self-reported constipation was consistently higher than that defined by the Rome II criteria.[22] Figures from a North American review paper estimate that, in addition to the 63 million people meeting the Rome II criteria for functional constipation, a further 50 million reported that they had constipation. The authors of the review suggest that these differences may reflect the lay perceptions and expectations of normal bowel function, in particular frequency.[24] In line with the STOOL report findings,[19] it was the absence of a daily bowel movement that people described as 'being constipated'. Evidence from the literature surrounding irritable bowel syndrome suggests that the Rome criteria are not used to any great extent within routine clinical practice in primary care, with estimates of between 12% and 20% of GPs knowing the criteria and only 3–4% using them.[25,26]

Lay definitions

Frequency of bowel movements is an often-used lay criterion, with most people associating constipation with decreases in normal frequency of bowel movements. Within 'frequency of bowel movements' there are at least three distinctive experiences:

1. those who are unable to pass a stool despite having an urge to go ('can't go')
2. those for whom there is an infrequent passing of stools ('not going to the toilet')
3. those who miss a day without a bowel movement ('not going as often').[19]

In a UK-based study of hospital outpatients, almost one-half of the participants thought of constipation purely in terms of frequency of bowel action, without considering difficulty or pain on defecation.[27] The importance attached to the frequency of bowel movements is not just a UK finding, with both Japanese[28] and Australian[17] studies finding it to be of the highest importance[28] to older people, and the most often cited description of constipation.[17]

The STOOL report highlights the range of factors taken into account when people define constipation.[19] In addition to frequency, when defining constipation lay people place emphasis on a range of other symptoms, such as straining,[29] bloating[30] and unsatisfactory defecation.[31] To further add to the complexity of the lay definition of constipation, the importance, or implicit weighting, attached to different symptoms, or combinations of symptoms, varies from patient to patient.[17,19,28]

Prevalence rates of constipation among older people

Given the lack of consensus on the definition of constipation in the clinical world, and the variation in definition and perceptions of constipation among lay people, it is not surprising that there is little agreement on the prevalence rates of the condition. UK estimates of prevalence rates of constipation in the general population range from 2% to 51.5%.[13,15,32–34] In the epidemiological study in North America mentioned earlier, prevalence rate estimates range from 1.9% to 27.2%.[24]

Regardless of this lack of consensus over actual prevalence rates, there is agreement that the rates do increase with age[5,35,36] (*Table 1*). In the HTA-commissioned systematic review of the effectiveness of laxatives in the elderly, the authors assert that approximately one-fifth of older people living in the community have symptoms of constipation.[1]

TABLE 1 *Consultation rates in primary care for constipation in the over-45s*

Consultation rates/10,000	Age range of patients (years)
75	45–64
200	65–74
400	77–84
600	85+

Adapted from McCormick *et al.*[37]

Impact of constipation on QoL in older people

Given the prevalence and burdensome nature of chronic constipation, the literature surrounding the impact it has upon QoL and standardised assessments to measure this is surprisingly sparse.[38] Many of the early studies attempting to investigate the overall burden of chronic constipation on QoL made use of general assessments such as the Gastrointestinal Symptom Rating Scale and the Psychological General Well-Being Index.[3] These assessments have been limited, however, to observational studies and cross-sectional comparisons.

Psychological General Well-Being Index scores (which assess anxiety and depression, perceived health, vitality, and overall well-being) were significantly lower (poorer) for people with constipation than the published scores for a general population sample.[3] In a cross-sectional, population-based survey of individuals of at least 65 years of age completing the Medical Outcomes Study Short Form General Health Survey, those with chronic constipation reported poorer role functioning and pain scores compared with those without constipation.[2] A similar pattern was shown in a mailed survey that assessed health-related QoL (HRQoL) (using the Short Form questionnaire-36 and Short Form questionnaire-12 items) among a Canadian population with self-reported functional constipation (Rome II criteria), when compared with Canadian norms.[39] In interviews with frail older people living at home, constipation was considered by 11% to be a major problem adversely affecting their QoL.[21] Although there is a paucity of them, studies that report the relationship between QoL and constipation show that people with constipation generally have impaired QoL compared with the general population.

Management of constipation in older people

The most common method to treat constipation in older people (> 50 years) is to use laxatives. However, there is little evidence to support either their clinical effectiveness or cost-effectiveness.[1] Readers interested in the evidence (or lack thereof) for the use of laxatives in the management of constipation in older people are encouraged to read the Health Technology Assessment (HTA)-commissioned review,[1] Gallagher, O'Mahony and Quigley's recent review[40] and the STOOL trial report.[19]

While there is little evidence supporting the use of laxatives in the treatment of constipation in older people, there is also little evidence-based guidance on what constitutes effective management of constipation in older people more generally.[1,41] The HTA review concludes that laxatives may not be an appropriate method for treating constipation for all people, and that change in general diet may be sufficient to treat and/or prevent the condition. However, the authors concede that there is a lack of good-quality evidence showing that dietary interventions are effective.

Petticrew *et al.*[1] proposed a stepped approach to the management of constipation, which first considered dietary and lifestyle changes then (if unsuccessful) considered dietary supplements, and then (if both of the previous interventions failed) considered the use of a prescribed cost-effective laxative treatment.

Taking into account the findings of the review, the advisory panel to the HTA proposed a further step in the constipation management strategy. This step involved prescribing a single class of laxative (bulk, stimulant or osmotic laxative) in the first instance and then, if this failed to resolve the constipation, adding in a second laxative from another class (e.g. stimulant plus bulk). In light of this, the HTA commissioned two independent randomised controlled trials (RCTs) – STOOL and LIFELAX.

The STOOL trial[19] was commissioned to investigate the clinical effectiveness and cost-effectiveness of laxatives prescribed for older people from the three classes (bulk, stimulant or osmotic laxative) and for different management strategies of combining the classes.

LIFELAX was commissioned to compare the clinical effectiveness and cost-effectiveness of practice-based educational interventions to change the diets of older people who have constipation with traditional medical management using laxatives.

Impact of diet and lifestyle on constipation

Interest in the role of dietary fibre has existed from the Victorians, who believed that bran stimulated colonic movements. By the 1900s, fibre had received some attention for its role in relieving constipation, and in the 1930s dietary fibre was being investigated for its laxative properties.[42]

Epidemiological evidence suggests that diseases of the large bowel, commonly seen in industrialised countries, are linked with decreasing fibre intake.[43] Findings from the recent European Prospective Investigation into Cancer and Nutrition study have suggested that where there is a low average fibre intake, doubling total fibre intake from foods could reduce the risk of colorectal cancer by 40%.[44]

Intake of dietary fibre is just one of a number of factors that influence bowel frequency.[45] The most common causes of constipation in primary care are related to diet, fluid intake and psychological factors.[8] Although there is 'no compelling medical evidence that inadequate fluid intake results in constipation', it is generally agreed, both by the medical profession and the general public, that low levels of fluid intake are associated with constipation.[10]

Constipation is more common in women than men and its prevalence increases with age.[46] In constipated older people, a lifetime of environmental risk factors, such as poor intake of dietary fibre, chronic use of laxatives and ignoring periods of high motility, rural living and colder temperatures are likely to have been causes of constipation.[45,47] Others have found evidence for gender (female), ageing, low energy intake, inactivity, number of medications taken, low income and low education level, as well as depression, physical and sexual abuse being factors associated with constipation.[48]

Constipation is rarely seen in developing countries and it has been related to the low-fibre diet consumed in the typical industrialised society.[43] From this brief introduction it is apparent that the impact of diet and lifestyle on constipation is multifactorial. A more detailed consideration of the evidence of these factors and summary of the evidence, as was incorporated into the LIFELAX diet and lifestyle advice, follows.

Fibre and constipation

'Fibre supplementation is generally the cornerstone of prophylaxis against constipation.'[29] Increasing stool weight and improving bowel movement are two of the primary physiological functions of the large bowel[49] in which dietary fibre has a role to play. Dietary fibre can be defined as a 'plant-derived material' that is 'resistant to digestion by human alimentary enzymes';[50] it affects the large bowel more than any other dietary component.[51]

Dietary fibre's relationship with the gastrointestinal (GI) tract includes roles of being a substrate for bacterial fermentation, water holding, cation exchange and adsorptive functions.[50] These mechanisms cause an increase in stool output and dilute the colon's contents.[51] The increase in faecal bulk depends upon the type of fibre ingested (e.g. wheat produces high faecal bulk compared with pectin).[52]

Adding sources of insoluble fibre to the diet significantly increases stool weight.[49] Wheat bran and oat bran, which are composed of differing amounts of insoluble fibre (> 90% and 50–60%, respectively), have similar effects on daily stool output, although they work by a different mechanism. Oat bran, which consists of more soluble fibre, results in greater bacterial growth than wheat bran, whereas the insoluble fibre of wheat bran provides more slowly fermentable polysaccharides to maintain the microbial population during transit through the large intestine. Neither oat bran nor wheat bran should be thought of as the superior 'treatment' for constipation, as both have important (if different) roles to play.

Results from a double-blind controlled trial to measure the effects of wheat bran in the treatment of constipation suggest that bran was effective in improving bowel frequency and large bowel transit time, and that a daily dose of 20 g of bran in addition to a high-fibre diet is beneficial to patients with chronic non-organic constipation.[53] Gear *et al.*[54] also concluded that a high intake of dietary fibre is associated with more rapid transit times.

Non-starch polysaccharides (NSPs) refers to all fibre in the diet. Recommendations as to the amount of NSP the average adult diet should contain suggest at least 18 g per day.[55] The Dietary and Nutritional Survey of British Adults[56] found that fibre intake was significantly greater in individuals from higher social classes, higher in men who did not smoke or drink and higher in older women. The National Diet and Nutrition Survey (NDNS)[57] of people aged ≥ 65 years reported, nonetheless, that the mean NSP intakes for free-living men and women (13.5 g for men and 11.0 g for women) were significantly below the dietary reference value, with intake decreasing with age. There was a positive association between the number of bowel movements and NSP intake in free-living men and women in the NDNS;[57] for women, this increased bowel movement with increased NSP intake was regardless of laxative

use. Analysis from the Nurses' Health Study[58] found a higher dietary fibre intake to be associated with a decreased prevalence of constipation.

Though a systematic review concluded that neither strong nor consistent evidence existed regarding the effectiveness of using dietary fibre for constipation in older adults, this, the authors conceded, was due, in part, to weak study design.[59]

Fluid and constipation

Whether or not fluid relieves constipation is a disputed fact. Health practitioners regularly recommend increased fluid intake to alleviate constipation, but the role of fluid has been challenged. Lindeman *et al.*[60] found no association between fluid intake and frequency of chronic constipation in the elderly, while Chung *et al.*[61] did not observe any significant increase in stool output by healthy volunteers when fluid intake was increased. There is, however, evidence which does suggest that increased fluid intake has a role in alleviating constipation. Klauser *et al.*[62] found that a relatively short period of fluid deprivation decreased stool frequency and stool weight in young healthy male volunteers. Positive associations between fluid intake and bowel movements were reported for women aged ≥65 years in the NDNS,[57] while no relationship between fluid intake and bowel movement frequency was seen in men and women living in institutions. It is important that when individuals are advised to increase their fibre intake they are also advised to increase their fluid intake.[63]

Probiotics, prebiotics and constipation

Probiotics and prebiotics both have a beneficial impact on gut microflora.[64] Prebiotics have an osmotic effect on the gut, as long as they are not fermented; when they are fermented by the endogenous flora they increase gas production.[64]

Gut bacteria, of which 400–500 species exist in the human large intestine, carry out fermentation, which metabolises endogenously produced and dietary residues.[65] Dietary carbohydrates that have not been digested in the upper GI tract are the main substrates for gut bacterial growth, in addition to amino acids, bacterial secretions, lysis products, sloughed epithelial cells and mucins, which are metabolised to produce short-chain fatty acids (SCFAs).[65] In summary, the positive influences of gut microflora is that they prevent colonisation by harmful bacteria, have roles such as improving lactose tolerance, providing SCFAs as energy substrates, neutralising toxins, stimulating the intestinal immune system and having a role in reducing blood lipid levels.

Probiotics, defined as viable non-pathogenic microorganisms, which, on ingestion, exert a positive influence on host health or physiology,[66] are either bacteria or yeast.[67] In a recent study,[68] 350 healthy elderly subjects consuming one, two and three 125-g servings per day of *Bifidobacterium* SP/DN-173010, had marked reduced transit time (22%, 40% and 47% reduction of initial values). This effect was still present for 2–6 weeks after the end of the product consumption.

Constipation was explored in a recent review of probiotics in human studies;[69] the authors reported that few studies were of double-blind design and had adequate washout periods. Sample size was often limited and outcome markers were non-comparable, including both bowel frequency and transit time. They concluded, however, that probiotics do have a probable effect on gut transit time and on stool frequency, although this is species and strain specific rather than genus dependent.

Described as non-digestible food ingredients, prebiotics stimulate selectively the growth and activity of bifidobacteria and lactobacilli, which benefit health.[70] Non-digestible oligosaccharides are found in plant cells naturally and are also manufactured food components, they are non-digestible (in the upper GI tract) and are prebiotics; two well-studied and well-established prebiotics are inulin and oligofructose, which are fermented by the beneficial flora (bifidobacteria and also lactobacilli) The major food sources of both inulin and oligofructose in the typical Western diet are wheat (70%) and onions (25%).[71] Evidence indicates that these fructans are digested in the large intestine, increasing microbial mass and producing SCFAs,[72] which also increases the stool mass, beneficial for bowel health.[51]

The laxative effect of prebiotics was shown by Gibson *et al.*,[73] in whose study oligofructose and inulin significantly increased stool output, possibly due to an increase in biomass. In constipated patients, low-digestible carbohydrates, with a low molecular weight, had a positive effect on intestinal transit time in constipated patients.[74]

An earlier study[75] examined the effect of fructo-oligosaccharides – found naturally in onion, asparagus root, artichokes and wheat – on gut health. Increases in bifidobacteria – believed to be beneficial to the host – following fructo-oligosaccharide ingestion, were found to relieve both constipation and loose stools, as well as improving blood lipid profiles.

The definition of dietary fibre alludes to the fact that it consists of 'remnants of edible plant cell polysaccharides and associated substances resistant to hydrolysis by human alimentary enzymes'.[76] Dietary fibre improves laxation by increasing stool weight from the fibre in the stools and also by bacterial cells (which have high water content). Higher faecal water content increases the ease of stool passing. Cherbut[76] described how inulin and oligofructose, found in a number of vegetables, fruits and whole grains, both fit into the current concept of dietary fibre and contribute to a well-balanced diet.

Kleessen *et al*.[77] observed that inulin and lactose improved the clinical signs of constipation on elderly constipated individuals whose bowel movements increased from one or two per week to 7.5 times per week with a 40 g/day intake of lactose and eight to nine stools per week with either a 20 g/day or 40 g/day dose of inulin. The elderly tend to experience an increase in bifidobacteria and a decrease in enterococci and enterobacteria numbers with inulin, which had a better laxative effect than lactose. Use of prebiotics that change the elderly patient's intestinal microflora, as seen in Kleessen *et al*.'s[77] elderly population, may be of benefit to the wider elderly population.

Exercise and constipation

There is perceived to be a lack of convincing data relating physical activity (or a lack thereof) to constipation.[29] Propulsive movements in the large intestine are increased by exercise.[78] Although it is thus assumed that increased activity stimulates bowel motility, an investigation on healthy young men failed to confirm this;[79] however, mild exercise accelerated mouth–caecum transit time for a liquid-based meal by 20–25%.[80]

In patients with chronic idiopathic constipation, 4 weeks of regular moderate physical activity did not alleviate slow transit constipation.[81] The authors of this study suggested that more vigorous activity, for a longer time period, might have shown more positive results, but compliance in an elderly population may have been reduced with a requirement for increased vigour.

In women aged 36–61 years, increased physical activity was related to a reduced prevalence of constipation;[58] taking part in physical activity daily was independently associated with a 44% lower risk of constipation, while physical activity two to six times per week was associated with a 36% lower risk when compared with less than once daily.[58]

A daily walking programme, within 30 minutes after a meal has been recommended, with stationary exercises for those who cannot walk.[29] The authors[29] suggested that abdominal and pelvic floor strengthening exercises may be useful.

Position for defecation

In industrialised societies the preferred position for defecation is seated, while in Asia and Africa the main position is squatting. In a study carried out in individuals with normal bowel habits, the squatting position required less time and less straining for faeces depletion than any other sitting position.[82] In the squatting position the rectoanal junction is straightened, whereas in the seated position more straining is required to push the faeces through the right rectoanal junction.[82] The strain required to defecate in a seated position may lead to repeated Valsalva manoeuvres (forcibly exhaling against the closed airway) and may result in defecation syncope and death, while the squatting position is associated with reduced amounts of straining.[83]

Summary of diet and lifestyle advice for the LIFELAX trial

- Most people experience constipation at some point.
- 'Normal' bowel movement frequency is from three times/day to three times/week.
- Signs of constipation include:
  - hard stools that are difficult to pass
  - frequency of stools decreasing
  - cramp-like pains in lower abdomen.
- Constipation may be caused by:
  - not eating enough fibre (fruit, vegetables and cereals)

  - not drinking enough fluid
  - poor bowel habits (ignoring the 'call to stool')
  - medicines (antacids, codeine, iron tablets, some antidepressants).
- Constipation is made worse by:
  - dehydration
  - inactivity
  - painful anal conditions (e.g. haemorrhoids).
- Constipation can be eased by:
  - eating regularly
  - eating more fibre-rich foods (fruit, vegetables and cereals)
  - drinking eight to ten cups of water/juice/soft drinks per day
  - keeping active/regular exercise.
- Toileting:
  - sitting in a comfortable position
  - spreading your legs slightly apart and leaning forward
  - relaxing and taking your time.

Behaviour change

The nutritional evidence-based guidelines that underpinned both the standardised and personalised intervention arms were the same, and it was in the style and mode of delivery that the arms varied. Not all of the findings of the studies we used to inform the intervention were appropriate for both arms. Full discussion of the literature reviewed, and the theoretical approaches and models used to inform the behaviour change interventions used in LIFELAX, can be found in Chapter 3, which details the development of the intervention.

We were seeking to develop two notionally different interventions in LIFELAX. One of the arms (standardised) needed to sit firmly within the current nursing model in the UK[84] and be suitable for delivery within a routine appointment time. The other arm (personalised) was informed by techniques that had been shown to be effective in interventions of behaviour change in similar topic areas with similar samples to ours.

In studies of individual behaviour change strategies, particularly those relating to dietary change and exercise,[85–87] personalised interventions have been shown to be more effective than standard, non-customised approaches. Personalised interventions, however, are typically more resource intensive than non-individualised approaches.[88]

Summary

Although it is often viewed as a trivial complaint, constipation is undoubtedly a major concern to both patients and the health-care system. For an intuitively simple condition, defining constipation continues to prove difficult. Among health professionals, there is little consensus on a formal definition of constipation. The Rome II (and more recently the Rome III) criteria were an attempt to formalise the assessment of constipation yet as we have seen, they are complex and few practitioners use them in practice. Rather, in clinical practice, constipation tends to be a subjective diagnosis. Frequency of bowel movement is an important factor in the assessment of constipation yet there is no consensus on how often the 'normal' bowel opens. Clinicians do agree, however, that there is a wide variation between individuals in the 'normal' frequency of bowel movements, ranging from three times per day to three times per week but many patients have expectations of a daily bowel movement.

Lay perceptions of constipation are far removed from the Rome II criteria though, as with health-care professionals, frequency of bowel movements is a key component of the definition of constipation for the majority of older people.

The Petticrew *et al.*[1] review found that there is little known about the clinical effectiveness and cost effectiveness of laxative treatment for constipation, although dietary and lifestyle changes may help in the prevention and treatment of constipation, there is also little clear evidence about the cost effectiveness of such management strategies.

Collectively the STOOL[19] and LIFELAX trials were designed to provide such evidence. It is sad to report that given the recruitment difficulties in both trials, clinical trials to evaluate the clinical effectiveness and cost effectiveness of these treatments remain to be done in the UK.

Embedded qualitative process evaluation

Randomised controlled trials and process evaluation studies are complementary research methodologies.[89] Although the former excel in producing outcomes data, the latter provide procedural information, such as the fit between the study protocol and how the research is practically carried out.[89,90] Oakley[90] describes the typical

functions of embedded process evaluations in detail:[90]

> Process evaluations within trials explore the implementation, receipt, and setting of an intervention and help in the interpretation of the outcome results. They may aim to examine the views of participants on the intervention; study how the intervention is implemented; distinguish between components of the intervention [and] investigate contextual factors that affect an intervention. Process evaluation can help to distinguish between interventions that are inherently faulty (failure of intervention concept or theory) and those that are badly delivered (implementation failure).
>
> (p. 413)

Process evaluations are therefore particularly useful within RCTs of complex interventions, when it may be difficult to identify the active components of the interventions from contextual 'noise'.[91] Examples of RCTs incorporating qualitative process evaluations include the Southampton Heart Integrated care Project (SHIP) in which the evaluation contributed towards interpretation of the research findings, and the Birmingham Rehabilitation Uptake Maximisation Study (BRUM), in which the evaluation provided insights regarding reasons for non-adherence.[92–94]

Within the LIFELAX RCT, a qualitative process evaluation was used to collect data on the development and implementation of both the RCT and its interventions. Whereas in previous studies, process evaluations have largely functioned as auxiliary studies, supplementing the research findings of their host trials, in LIFELAX the process evaluation took a subtly, yet fundamentally broader, role by examining the process of HTA in action, through the medium of an RCT. In this respect the research questions were designed not to ask 'how closely does implementation of the interventions fit the protocol?' but 'how is the protocol constructed and practically enacted, and what are the implications for the types of knowledge produced?' The process evaluation was thus fully integrated into the RCT, rather than playing a complementary role; its results contributed information about the process of evaluation, the barriers faced by the trial team, the manner in which some of these barriers were circumvented, and the overarching structural problems that eventually prevented the trial's completion.

Understanding the process of evaluation is important, for we actually know little about the practical conduct of HTA through RCTs, although there is a large and expanding body of literature that details either the RCT's methods or the results of their application. In one specific field of HTA – the development and evaluation of 'telehealthcare' systems – May *et al.* have undertaken a series of studies[95–98] that have examined the evaluation of a relatively unstable health technology using RCTs and other methods, and have developed a model of the social and technical process of HTA that defines the contingent points on the journey between ideation (i.e. the emergence of ideas about the value of a new technology) and normalisation (i.e. the point at which it becomes possible for it to be embedded in clinical practice).[99] Of specific interest here is the way that evaluation acts as a mediating set of practices between these two points on the 'innovation journey': specifically, the production of evidence supports – or hinders – the uptake of a new technology.

Evaluation is not a discrete asocial activity, nor is it self-evident. At the very outset, we place the kinds of evaluations that define the specific utility of health technologies within the frame of the larger 'proto-discipline' of HTA. HTA is one of the major research enterprises of our time. Broad in scope, and defined by its emphasis on formal – mainly quantitative – methods and its focus on clinical effectiveness and cost-effectiveness, HTA is directed at the production of evidence about the efficacy and utility of techniques and technologies of health-care delivery treatment modalities and ways of working. As a field of practice, HTA is orientated around the production of evidence that meets particular criteria of adequacy[100,101] – its formal proof, as it were, is to be found in the outcomes of the RCT, systematic review and meta-analysis. The questions that inform it tend to arise directly from the thrust of health-care policy, and the outcomes of HTA practitioners' work are specifically intended to mediate between policy and practice. So within the field of HTA, it is method that is prioritised either in the production of primary outcomes data or in the synthesis of existing knowledge.[102] The expository literature of HTA reflects the priority given to methods, not theories, by locating them in a rhetoric of political and social neutrality, and emphasising applied investigatory technique over broader political questions. None of this is intended to imply that practitioners of HTA are unaware of the political implications of their work or the wider social implications of their practice – the reverse is

certainly the case. But HTA emulates the neutral rhetorical form of the wider field biomedical science, constructing apparently methodologically secure quantitative facts. So it has, at the outset, a first line of defence against wider political critique – it is given as quantitative science rather than politics.

In this broad context, HTA can be seen as the development of a field of research practice that accords well with contemporary notions of the place of 'research' in the complex political and social contexts of the advanced economies. For example, it fits well with the model of Gibbons *et al.* of 'mode 2' knowledge production through its connectedness with 'user' communities, its multidisciplinarity and because of the permeability of the institutional structures in which it is located.[103] Certainly the evaluation of new systems of working and of the delivery of treatments is not simply directed at establishing their fitness for specific tasks, but about adjudicating on their superiority over others. More than this, it is focused on evidence production: HTA is thus one of a number of regulatory systems of practice available to governments and others in the advanced economies to constrain the conduct of health professionals and health-care institutions. It can be understood as a form of institutional surveillance that governs the conduct of practice, defines the directions of innovation, and defines potential new fields of clinical organisation and practice. As Tanenbaum[104] has observed, the thrust towards outcomes studies within the field of HTA (and across biomedicine more generally) can also be seen to represent a powerful and authoritative social movement.

Relevant work to conceptualise HTA to date has mainly been directed either at practical problems of recruitment into trials,[105–111] or at macrolevel analyses of the relationship between policy formation and evidence production.[104,112] More localised critiques have investigated the assumptions that underpin outcomes themselves or the methods by which they are reached.[95] Much less work has investigated the specifics of HTA as a field of practice, the sociotechnical networks in which knowledge about efficacy is defined and generated, negotiations about criteria for its adequacy or the procedures through which these are enacted in concrete practices. The paucity of literature in this field is surprising, given the importance of the RCT as an HTA method. The process evaluation was necessary to provide a more detailed understanding of the organisation of RCTs, and to assist in the development of a robust theoretical model of HTA practice.

Chapter 2
Trial design

Overview

LIFELAX was designed as a pragmatic[113] three-armed cluster (randomisation at the level of the individual general practice) RCT to compare laxative treatment (current practice) 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 one long consultation – or two shorter consultations – with telephone reinforcement) in the management of chronic constipation in older people. LIFELAX was to be conducted in north-east England and was to recruit patients aged ≥55 years, registered with practices participating in the trial, with a current diagnosis of functional constipation (operationalised as either having a recorded diagnosis of functional constipation or having received three or more prescriptions for laxatives in the preceding year). Due to poor levels of practice uptake and lower than expected levels of patient recruitment, it was necessary to approach the HTA for an extension to the LIFELAX trial and these eligibility criteria were revised in the subsequent protocol amendments. In Chapter 4, which details the implementation of the LIFELAX trial, we describe the protocol revisions in depth. Here we will describe the design of the trial as it was in the original protocol, agreed with the HTA and submitted to the Multi-Centre Research Ethics Committee (MREC). The original protocol (version 2, 4 October 2004) and the final version (version 5, 24 July 2006) can be found in Appendix 1.

Objectives

The primary objectives for the study were to investigate the clinical effectiveness and cost-effectiveness of:

1. laxatives versus dietary and lifestyle advice
2. standardised versus personalised dietary and lifestyle advice.

Health technologies being assessed

Treatment strategies at the patient level

LIFELAX was a cluster randomised trial. Practices were randomly assigned to one of the three treatment strategies, with all patients in the practice then getting their practice's allocated strategy. Within the laxatives arm, free choice of class and dose of laxatives were allowed as there was insufficient evidence[10,114] 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 more closely replicated the situation in routine clinical practice, therefore participant adherence to treatment protocol was expected to be better than should a change in drug have been required. For similar reasons, leeway in dosage was permitted within dose ranges commonly used in clinical practice. To minimise the risk of prescribing subtherapeutic doses, the practice training/initiation reminded participating health-care professionals of the therapeutic dose ranges for the available laxative preparations.

The dietary and lifestyle interventions were informed by findings from previous trials of diet and lifestyle interventions.[85,87,115,116] They drew upon theories of individual behaviour change, including the concept of self-efficacy[117] and the stages-of-change model.[118]

For the personalised intervention arm, a series of information leaflets on a range of topics were developed and tested.[119] These comprised eight patient information leaflets (PILs) on constipation, activity, bowel health, fruit and vegetables, fibre, fluid, alternative therapies and laxatives (see Appendix 3). In the standardised arm, participants were given a general constipation PIL. Copies of the materials produced can be obtained from the lead author.

In both of the diet and lifestyle intervention arms, the training package was designed to be delivered by practice nurses, community nurses or other

appropriate health-care professionals (according to local custom). Appointments were generally offered at the surgery, although home visits were an option where appropriate. In the standardised, non-personalised arm, there was a single short (approximately 10 minutes) appointment, with delivery of a standard pack of information and brief and general explanation of the information leaflet. In the personalised arm, there was an initial long (30–45 minutes) appointment (though this could be undertaken in two shorter appointments 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'[88] – was undertaken. The personalised approach included a patient-specific assessment of barriers to and facilitators of change and delivery of a personalised pack of information with individual targets (tools were developed to assist nurses with setting personalised goals and plans). Patients in this arm received a follow-up motivational telephone call from the nurse at 1 week and 1 month after initial appointment.

A potential threat to patient recruitment and retention in this trial was patients' unwillingness to forgo medication. For this reason, although diet and lifestyle was the first-line treatment for patients allocated to those arms, the option of continuing laxative use [either prescribed or over the counter (OTC)] was available if required; the need for and use of such medication was captured as part of the evaluation process.

Although a 'washout period' is recommended in trials in functional GI disorders[120] the clinicians and dietitians involved in the design and management of LIFELAX took the decision not to implement this. There was a concern that patients would be reluctant to withdraw from any laxative regimen that was currently effective before embarking on any diet and lifestyle changes, and that this would have a negative impact upon recruitment. There was also a concern that even without a 'washout' period – as diet and lifestyle alterations typically take time to show change in bowel function – participants may see this as a failure of the intervention and not adhere to the protocol or withdraw. In light of this, participants in the diet and lifestyle intervention arms of the LIFELAX trial were able to continue to use laxatives (prescription or OTC) should they or their GP feel it appropriate, while those in the laxative arm continued to take their usual laxatives as prescribed.

Training strategies for health professionals

An orientation and training programme was developed for the practices recruited to the study. All practices had an on-site training visit to discuss aspects of the treatment protocol and how it was to be delivered in the practice. In addition, a dietitian with experience in health promotion delivered 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 (GPs, practice and district nurses, and health visitors) in the practice were invited to a single 1-hour session to introduce the programme and the patient resource pack.
- *Personalised dietary and lifestyle intervention* All primary health-care professionals in the practice were invited to an initial 1-hour session to introduce the programme and the patient pack. Practice staff involved in delivering the intervention to patients were 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 was based on experience in other similar studies, and represented a balance between minimising the demands on busy health professionals' resources, while 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,[121] suggested that in-practice delivery of training of this nature is more cost-effective than delivery at a single central location.

Study participants

Target population

The target population for the study was people aged ≥ 55 years (reduced to 50 years after protocol amendment) with chronic functional constipation, living at home. This 'age' choice was made after due consideration of the morbidity statistics from general practice,[5] which indicated that GP consultation rates for constipation rise rapidly in the 45- to 64-year age group and continue to rise steadily with age. The exclusion of residents in long-term care reflected the different morbidity and the lack of autonomy over decisions pertaining

to diet and lifestyle changes and lifestyle experience of long-term care residents. LIFELAX focused on a predominantly ambulant population able to attend independently a primary care clinic.

Inclusion criteria

The complexity of the Rome II criteria for functional constipation[122] militates against their use in screening for chronic constipation. Moreover, newly incident cases of constipation, especially among older adults, should be investigated to determine the underlying cause of the constipation and to eliminate more serious problems[123] before laxatives are prescribed. LIFELAX therefore identified and recruited only 'prevalent' cases, defined primarily in terms of those prescribed laxatives three or more times in the previous 12 months, or with a recorded diagnosis of functional constipation (although it was unusual to find such a diagnosis consistently recorded and coded). Participants meeting this criterion were identified from general practice computerised patient records using an electronic 'query' (the electronic query was designed to work with the EMIS practice computer system to interrogate repeat prescribing databases). It was recognised that the relapsing and remitting nature of constipation meant that not all patients thus identified would be constipated (by objective or subjective criteria) at any given time.

Patients who fitted one or more of the following criteria were therefore eligible for the trial:

1. a recorded diagnosis of chronic functional constipation
2. prescribed laxatives three or more times in the previous 12 months
3. prescribed a laxative (or combination thereof) continuously for the previous 12 months.

Exclusion criteria

1. Patients resident in long-term care.
2. Patients with inflammatory bowel disease, intestinal obstruction/bowel strictures, known colonic carcinoma, and conditions contraindicative to the prescription of laxative preparations.[124]
3. Inability to read and understand written treatment plans and educational material.
4. Inability to complete outcome assessments, even with assistance (e.g. major cognitive impairment, lack of understanding of English).
5. Patients using opioid analgesics.

Consent

Favourable opinion from MREC was granted, although the request from the chief investigator (CI) for 'no local investigator status' was not approved. (For a full account of the trial's status as 'site-specific exempt' see Chapter 4.) The implication of this was the need for a favourable opinion to a site-specific assessment (SSA) for each individual primary care practice (site) from appropriate Local Research Ethics Committees (LREC). Written informed consent was obtained for all participants recruited to the trial. All the patient recruitment materials followed Central Office of Research Ethics Committees (COREC) guidelines. The trial team used its experience from previous studies, where it had been felt that the COREC guidelines for information sheets led to a large, burdensome and often-intimidating document, and produced a short, succinct version to accompany the full version. A full patient information sheet (PIS) (version 6, 24 July 2006) (see Appendix 2) and a brief information leaflet (version 5, 26 May 2006) (see Appendix 2) were provided to send to patients via their GP. Patients were given time to consider the trial fully and ask any questions about the implications of the trial as part of the consent process.

Sampling design and implementation

Sample size

Participating practices were randomised to one of three arms. In calculating sample size for cluster randomised trials,[125] it was necessary to take into account within-cluster variance, measured by an intraclass correlation (ICC). Our experience in previous studies suggested that ICCs of 0.05 for QoL outcomes were typical.

Preliminary analysis of data from the average-sized practices of one of the applicants suggested that there would be approximately 40 patients in such a practice meeting eligibility criteria. We recognised that patients in practices allocated to the diet and lifestyle arms of the trial might be reluctant to undertake a change to their diet or lifestyle and might therefore withhold consent to participate. It was in anticipation of this risk that we made the assumption that only 30 out of 40 patients identified (75%) would agree to participate and that only 25 would provide follow-up data for 12 months.

Our primary outcome was a continuous variable score on a QoL scale. In the absence of detailed data on the distribution of QoL scores in our population, we were able to specify, nonetheless, the effect size that we wished to detect. We arbitrarily set this at 0.3 standard deviations on the condition-specific QoL scale.[38] Within the literature on QoL assessment, there has been a growing consensus[126] that an effect size (i.e. change over time divided by standard deviation at baseline) of < 0.2 represents a 'negligible' change, an effect size of 0.2–0.5 represents a 'small' effect, an effect size of 0.5–0.8 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 represented 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 was not a comparison of an intervention with placebo or with normal practice. Instead, there were three active treatment groups. It is not unreasonable to assume that we might have observed at least a small change over time in symptom-related and QoL outcomes in all of these treatment groups. What we were primarily interested in was 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 ICC of 0.05, and the ability to recruit and retain 25 patients per practice, we therefore needed a total of 57 practices (19 per arm).

Recruitment

Practices

General practices in England and Scotland, UK, were invited by letter to participate. As the STOOL Trial[19] was recruiting practices in the north-east of England at the same time as LIFELAX, we were careful to divide up the Primary Care Trusts (PCTs) so that the same practices were not approached by the two studies. When the STOOL Trial closed, personal approaches were made to the practices that had expressed interest in STOOL by the STOOL trial manager in a bid to 'convert' them to LIFELAX. The remaining (non-recruited) practices in the PCTs eligible for the STOOL trial were then approached by the LIFELAX team. It was felt that LIFELAX would be more appealing than STOOL to practices as there was a range of relevant training that accompanied the interventions, and therefore that practices which had not been willing to participate in STOOL might nonetheless be agreeable to take part in LIFELAX. All practices that wished to join LIFELAX were then randomised into one of the three trial arms. As each practice was recruited to the study it was allocated a study identification number by the research team. This together with a measure of the practice size (number of partners) was then passed to an independent statistician who then generated the treatment allocation using electronically generated random numbers. The research team were kept blind to the randomisation algorithm that was used (the probability that a practice was allocated to a particular treatment depended on the size and number of practices previously allocated to each of the treatment arms). We recognised that practices may have had preferences with respect to allocation of intervention arm. We made it clear to the practices approached to participate in LIFELAX that allocation to intervention arm was completely at random and that practice preferences could not be taken into account.

Note: details on rounds of recruitment and Trusts approached can be found in Chapter 4.

Participants

LIFELAX recruited only prevalent cases that were retrospectively identified through computerised records of laxative prescriptions, as described above. The electronic query was offered to all practices. However, many surgeries did not use the EMIS system and others preferred to run the searches manually. Patients were initially screened by practice staff to remove those identified as ineligible for the study by reference to exclusion criteria. Eligible participants were then invited to attend a practice nurse-led research clinic to discuss entry into the study. Following informed consent, a baseline assessment (a face-to-face interview and self-completion questionnaire) was completed. A copy of the signed consent form was

posted back to the study team. The completed baseline assessments were posted back in a separate envelope. Following consent, the practice nurse contacted the study team and released the personal details of recruited patients. (This model of patient recruitment was the one used by the STOOL trial after several iterations of their approach to MREC to gain a favourable opinion. It proved to be rather time-consuming and burdensome to practices. As such, a different model was introduced after a major protocol amendment. This is covered in Chapter 4.)

Minimising bias and improving compliance

The commitment of GPs and practice staff was known to be crucial to the success of the study. Educational events were used to introduce the study protocol to health professionals from the participating practices. Regular updates on the study were included in Trust newsletters and also in the Northern Primary Care Research Network (NoReN)/Northern and Yorkshire Primary Care Research Network (NYReN) newsletter. Financial support was provided to practices to identify and recruit patients. Service support costs and excess treatment costs secured through the Support for Science (SfS) funding stream meant that there was be no financial 'cost' to practices for participating in the study. All study-related tasks were reimbursed at a generous level. Though a practice would not be able to look upon LIFELAX as a money-making activity, it would not be a drain on its resources.

The risk of recruitment bias (i.e. patients being unwilling to enter the trial because they may have to forgo their laxative treatment) was recognised. We believed that the availability of 'rescue' medication for patients randomised to the diet and lifestyle arms would reduce the risk of non-consent or loss to follow-up, due to anxieties about not being able to use medication. Likewise, the provision for continuing with an established and preferred laxative regimen in the laxatives arm was felt to increase the likelihood of participation and compliance.

Both at the point of recruitment and intervention initiation, the importance of adherence to the course of treatment, and of completion of questionnaires and diaries, was stressed to participants. Up to two written reminders were used for participants who failed to return postal questionnaires.

For LIFELAX, an intention-to-treat analysis was adopted, as it was important that we were able to estimate the extent of non-adherence by participants. We addressed this issue by collecting data about laxative use (both prescription and OTC) as part of the participants' daily diary and in follow-up questionnaires.

Baseline and outcome measurement

Participants were followed up for 12 months from the date of intervention initiation. Follow-up data were captured through a daily self-completed structured diary (for 6 months), and telephone interviews and self-completed postal questionnaires at 3-, 6- and 12-month time points (*Tables 2* and *3*).

QoL and clinical outcomes

The primary outcome, and the criterion upon which the sample size calculations were based, was patient-reported condition-specific QoL at 3 months post recruitment. Our preferred measure of QoL was the constipation-specific Patient Assessment of Constipation-Symptoms (PAC-SYM)/ Patient Assessment of Constipation-Quality of Life (PAC-QOL),[127] which had been demonstrated to have good validity and reliability. Permission to use this instrument was granted by the owners of the scale (Janssen Pharmaceuticals, Titusville, NJ, USA) after agreement that anonymised patient data (i.e. questionnaire responses) would be submitted to them for the purposes of further refinement of their scales and development of population norms. However, this measure is not utility based. For the purposes of the economic evaluation, a measure of the utility placed by patients on their health state was required. The condition-specific measure of QoL was therefore supplemented by the generic utility-based European Quality of Life-5 Dimensions (EQ-5D).[128,129] Secondary outcomes included bowel movement frequency, the presence/absence of the other Rome II criteria for constipation, patients' own perceptions of whether or not they were constipated, patient satisfaction with bowel function, adverse effects of treatment; relapse/ reconsultation rates, and fluid and fibre intake. In addition, the cost implications of the condition and its treatment (e.g. GP consultations, purchase of prescribed and OTC medication) was assessed, as part of the economic evaluation.

TABLE 2 *Baseline and outcome measures*

Outcomes	Measurement method	When	Where
Primary outcome			
HRQoL	Postal questionnaire	At 3 months post recruitment	Participant's home
Secondary outcomes			
HRQoL	Postal questionnaire	At 6 and 12 months post recruitment	Participant's home
No. of bowel movements per week	Self-completed structured diary + postal questionnaire	Daily for 6 months At 12 months	
Other Rome criteria: straining at defecation, stool consistency, perceived incomplete evacuation	Self-completed structured diary + postal questionnaire	Daily for 6 months and for 1 week at 12 months At 12 months	
Subjective perception of whether constipated; satisfaction with bowel function	Telephone interview + postal questionnaire	At 3 months At 6 months and 12 months	
Adverse events: abdominal pain, nausea, bloating, flatulence, diarrhoea	Self-completed structured diary + postal questionnaire	Daily for 6 months and for 1 week at 12 months At 12 months	
Use of prescribed and OTC laxatives	Self-completed structured diary + postal questionnaire	Daily for 6 months and for 1 week at 12 months At 12 months	
Fluid and fibre intake	Self-completed structured diary + postal questionnaire	1 day per month for 6 months At 12 months	
Relapse rates, including repeat consultations	Self-completed structured diary, GP records	Daily for 6 months; 12 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 3 *Measuring treatment impact*

Impact	Measure	When	Where
Costs to participants of the condition and its management	Telephone interview	At 3 months At 6 and 12 months	Participant's home
Consultation rates and laxative prescriptions	GP records	End of 12-month follow-up period	General practices
Adherence to drug treatment	Health diary; telephone interview	Using different methods, at 3 months At 6 and 12 months	Participant's home
Patient satisfaction	Postal questionnaire	At 3 months At 6 and 12 months	
HRQoL, including utility-based assessment of health state	Postal questionnaire	At 3 months At 6 and 12 months	

Methods of data collection

Table 4 shows participants' pathways through the trial in the original recruitment protocol, the clinical assessments completed and data collection methods used at different points on the pathway.

Baseline assessment (T^0)

Prior to any assessments being conducted, each participant was able to speak on the telephone with a member of the research team and was invited to discuss any aspect of participation in the study they wish. An appointment was made at the practice for patients to meet a practice nurse, who took informed consent and undertook the baseline assessment. This assessment included a short, structured face-to-face interview and a self-completion questionnaire. Current bowel function, fluid and fibre intake, patients' self-perceptions of whether they were currently constipated, and levels of anxiety and depression[130] were elicited, and data on activities of daily living,[131] condition-specific QoL, laxative use (both prescribed and OTC) and personal criteria for successful outcomes ('how would you define "successfully managed constipation" '?) were collected. A weekly structured self-completed diary was left with the participant and details on how to complete it were given. After the consent and baseline assessment visit was complete, a second appointment was made for participants to start the intervention. Should patients decide to withdraw when they returned to collect either their laxative prescription or for their diet and lifestyle appointment, the practice notified the research team and all baseline assessment data and patient identification data were destroyed or deleted from the study database.

Daily diary

To minimise recall bias, data on bowel habits and symptoms based on the Rome II criteria[122] were gathered by a structured diary (tick box format), completed daily and returned each month for 6 months. This diary was developed and piloted in parallel with the qualitative study that accompanied the STOOL study. It was designed to capture information on the number of bowel movements, other Rome II criteria, adverse events, relapse rates, use of laxative, costs of food purchased or activities undertaken as part of any diet or lifestyle changes made, and any out-of-pocket expenses associated with constipation and its management. Based on previous experiences of similar diaries in studies with older people, we expected that 90% of diaries would be returned completed.[132,133]

Postal questionnaires

Follow-up self-completion questionnaires, with up to two reminders for initial non-respondents, were

TABLE 4 *Participants' pathways through trial*[a]

Activity
Potential participants identified from computerised practice databases using simple electronic query to flag individuals receiving prescriptions for constipation (three or more in previous 12 months)
Initial screen by practice to identify clear exclusions
Written invitation sent by practice; appointment date to give consent at practice set with patient
Consent given at practice; baseline assessments conducted. 'Intervention start' appointment made
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
1-week reinforcement telephone call from nurse to patients randomised to personalised diet and lifestyle advice
Intervention fidelity measure – a small sample of patients in the standardised and personalised intervention arms of the trial receive a short postal questionnaire to ask about the diet and lifestyle advice
1-month reinforcement telephone call from nurse to patients randomised to personalised diet and lifestyle advice
3-month follow-up outcome assessment (postal questionnaire) and collection of cost data and personal levels of success (telephone interview)
6-month follow-up outcome assessment (postal questionnaire) and collection of cost data and personal levels of success (telephone interview)
12-month follow-up outcome assessment (postal questionnaire and 1-week symptom diary); review of practice notes to abstract data on consultation rates and prescription patterns

a This pathway reflects the original protocol. The changes to it are described in detail in Chapter 4.

sent by post to arrive at T+3 months, T+6 months and T+12 months. These questionnaires contained the same items as the baseline self-completion questionnaire.

Follow-up telephone interviews

The follow-up telephone interviews were also administered at 3 months and at 6 months. They focused on (a) the participant's perceptions of the outcome/success of treatment and (b) the use of health-care resources, and out-of-pocket expenses associated with the use of those resources, including purchase of OTC medication to manage constipation. The interviews were conducted by a trained member of the research team.

Medical records

Previous experience suggested that data on consultation rates and prescribed medication could be gathered most accurately and reliably from medical records. Our intention, therefore, was to collect such data about all study participants from practice-based medical records at the end of the follow-up period. Based on experiences in previous primary care trials,[134,135] for efficiency in data capture, we proposed that this be done practice by practice at the end of the data-collection period. However this activity was not completed due to the premature closure of the trial.

Methods of data analysis

Analysis was to be on an intention-to-treat basis. No subgroup analyses were pre-planned. The data were to be analysed using mixed effects models, accepted practice for the analysis of data from cluster randomised trials.[125] Variation between practices and variation between patients nested within practices were to be fitted as random effects. The difference between treatment strategies (i.e. the three arms of the trial) was to be fitted as fixed effects. Most of the outcome variables [e.g. QoL scores, number of days with (or without) symptoms] were continuous and were to be analysed assuming a normal error structure. The dependent variable in each model was point of follow-up (3-, 6- and 12-month outcomes for QoL, symptoms and perceptions of bowel function, 12 months for consultation and prescription rates). For each patient, baseline data were to be included as covariates. The mixed models were to be used to generate interval estimates for the differences between alternative treatment strategies.

(Due to the poor recruitment rates, the planned analysis and economic evaluation described here did not take place. Chapter 5 describes the analyses agreed with the HTA after the decision was taken to close recruitment.)

Economic evaluation

Perspective of the evaluation

We planned to 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 had hoped to supplement this by an individual participant perspective. Our selected outcome measures included condition- and treatment-specific QoL and a generic utility-based measure of health state, measured at the individual level. We also recorded the costs of the condition and its management, which were met directly by the patients themselves.

Measure of benefits used and type of study

Considering all of the measures of effectiveness estimated within the clinical trial, a cost-consequence analysis[136] was 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, were to be presented in a disaggregated way. For each arm of the trial, the breakdown of costs and outcomes was to be listed in a tabular format; no summary measures were to 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 QoL is an important indicator of benefit in the treatment of constipation, and was 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[128,129] – was also to be used, to facilitate calculation of quality-adjusted life-years (QALYs). We were, however, aware of the concerns about the use of QALYs in devising resource allocation strategies between different age cohorts. Therefore, we aimed to apply already existing

'corrective' measures to the results we obtained, so that our findings would not have unfavourable implications for the funding of health technologies for older people.

Furthermore, we anticipated that the EQ-5D might not be sensitive enough to detect differences in the population being studied. Therefore, alongside this utility-based measure, we aimed to calculate discomfort-free days (DFDs) as a new measure of outcome. This measure included the impact on patients' well-being of unwanted symptoms due to both constipation and treatment side effects. It is a crude but meaningful measure of the patients' perceived effectiveness of treatment. DFDs were to be derived through the self-completed structured diaries. Severity of impact was to be graded in levels, and the number of days spent in each level of discomfort was to be calculated. This information was to be used to assess correlation with DFDs responses. We believed that the comparison of DFDs with EQ-5D utilities would 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 QoL, rather than on extension of life.

Design of the integrated qualitative process evaluation

Introduction

The aim of the integrated qualitative process evaluation was to develop a critical understanding of the social processes and practices implicated in the development, implementation and dissemination of a RCT within the field of HTA. Because the study was ethnographic, qualitative research techniques were used, and it was therefore not appropriate to set out our research questions in hypothetical form. However, at the outset, we addressed the following specific questions:

- *Formation* How are ideas about the appropriateness of health technologies and their clinical applications formed and mobilised in practice; how are the interests of consumers and other users defined and incorporated in the organisation of the trial?
- *Integration* How are specific clinical and methodological problems within an RCT identified and resolved within professional groups and networks; how is the trial integrated into the existing organisation of clinical service provision, and what professional and organisational dynamics are involved in this integration; how is participation in the RCT negotiated and understood by subjects?
- *Implementation* How are the production of results negotiated and organised within networks of researchers; how are its results mediated to the wider community and how is this negotiated and organised, both formally (through report writing and presentation), and informally; how are the mechanisms and results of the trial understood by subjects?

What lessons can be learned that will improve the organisation and conduct of HTA RCTs in the UK – and further afield? The study holds important implications for the organisation and conduct of HTA. It is important that its results can inform and develop both policy and practice.

Methods

The study design used the Normalisation Process Model (NPM), which had been developed through empirical work in the evaluation of telehealthcare systems in the UK.[137] The NPM is a useful means of identifying and explaining the socially-mediated factors that affect the implementation of new technologies in health-care settings.

Four primary groups of actors involved in the deployment of the RCT were targeted. These were (1) the trial team ($n = 11$), (2) senior clinical staff and practice managers at each site ($n = 6$), (3) the practice nurses enrolled in the trial to deliver the intervention ($n = 9$), and (4) recruited participants ($n = 23$). Collectively, we describe these groups as trial *contributors*.

Due to the concerns of the MREC that repeated multiple interviews of recruited participants or enrolled NHS staff might constitute harassment, we conducted multiple (follow-up) interviews with members of the trial team and single interviews with practice staff and participants. Data from the research team comprised transcriptions of project meetings and audio-recorded semistructured interviews, field notes written during periods of observation, internal and external correspondence, and formal and informal documentation. Audio-recorded semistructured interviews were used to provide data from primary care staff and trial participants. *Table 5* presents the types of data collected through the process evaluation.

TABLE 5 *Data collected through the process evaluation*

Interviews with trial 'contributors' (trial team, enrolled NHS staff and trial participants)	Trial team	***N* = 11**
	Practice nurses	***N* = 9**: personalised (BCC), *n* = 6; brief intervention, *n* = 3; control, *n* = 0
	GP/practice managers	***N* = 6**: personalised (BCC), *n* = 1; brief intervention, *n* = 4; control, *n* = 1
	Trial participants	***N* = 23**: personalised (BCC), *n* = 6; brief intervention, *n* = 11; control n = 6
Steering group meetings	Each lasting approx. 80–100 min	***N* = 4**
Trial team meetings	Each lasting approx. 150 min	***N* = 16**
Working group meetings	Each lasting approx. 90 min	***N* = 8**
Field notes	A	2003–4
	B	2005–7)
Additional meetings	Press release	***N* = 1**
Additional materials	Numerous e-mails, protocol documents, letters, etc.	

BCC, behaviour change counselling.

The data collected through the process evaluation were pooled and analysed as a complete data set. In this report we have drawn primarily on the interview data, as this facilitates a more concise account. However, in the analysis underpinning this report, all forms of data were utilised.

Recruitment strategy

Practices enrolled in LIFELAX were recruited to the process evaluation by a three-step process. Initially, information relating to the process evaluation was included in LIFELAX recruitment packs distributed by the trial team. When a practice had been identified as suitable for inclusion, a letter was sent to the practice manager or senior partner in accordance with previous methods of contact with that practice. The letter included a brief summary of the process evaluation and forewarned the staff that a researcher (BH) would contact the practice by telephone within several days. In addition, senior staff were asked to cascade the content of the letter to the practice nurses as per local custom. The final step in this recruitment strategy was to telephone the relevant member of senior staff and/or practice nurses to arrange an interview. In some instances it was not possible to speak to relevant members of staff on any given occasion, and repeated telephone calls were necessary. However, the availability of staff was hard to predict, and even when a time and date for a return telephone call had been made in advance, staff were not always available to speak on the telephone or asked to reschedule the call. Consequently, if staff had not expressed an interest in participating in the process evaluation after approximately four telephone calls to a practice, it was decided not to pursue the recruitment further at that site. The rationale for this decision was to both maximise the productive use of research time, and avoid undermining relationships between the practice and the trial team, and thus jeopardising the RCT.

During the opening phases of the RCT, the recruitment of practices ran behind intended targets. Consequently, at this point in the process evaluation, staff from all recruited practices were approached to take part in an interview. Towards the end of the trial, when recruited practices were distributed across the country, we purposively sampled practices according to their randomised allocation status and geographical location. Practices situated more than approximately 60 minutes drive from Newcastle, UK, were offered only a telephone interview rather than the option of a telephone or face-to-face encounter. Practices randomised to either of the two diet and lifestyle arms of the trial [behaviour change counselling (BCC) or brief intervention] were specifically targeted, as these conditions required the most input from practice staff. Unfortunately, relatively few practice staff were recruited to the process evaluation.

In following the research strategy outlined above it became apparent that in many practices the practice manager rather than a senior partner mediated between the trial team and the practice. While senior partners ultimately made the decision for their practice to participate in the RCT, their general involvement in the trial was limited, although possibly also included the screening of patients for contraindications and comorbidity. Only two senior clinicians were recruited to the process evaluation. With regard to senior practice staff, including practice managers, we observed that during interviews these staff usually struggled to discuss the research beyond the reason for the inclusion of their practice in the RCT. While these explanations were of interest to the research team, the senior staff viewed their lack of practical involvement in the trial as a limit for the scope and value of the interview. Therefore, we found it difficult to reach many senior staff and after a period of time questioned the value of pursuing interviews with this group. It would be inaccurate to claim therefore that saturation of data occurred within the sample, although meaningful data were nevertheless collected.

At their recruitment to the RCT, participants were informed about the purpose of the process evaluation, and the possibility that they might be asked to partake in an interview. All participants were given the opportunity to have their preferences recorded if they preferred not to be contacted. At the initial stages of the LIFELAX trial all participating patients who had not objected to being contacted were sent a recruitment pack for the process evaluation. This included an information sheet and a response slip. Once response slips had been obtained from the participants, those willing to be contacted by the research team were telephoned to arrange a time and place for an interview. In the latter stages of the trial, due to the over-representation of participants within the brief intervention arm, we approached all participants recruited to the trial with the exclusion of those randomised to this condition. As it was not possible to conduct repeat interviews with individual participants – due to concerns by the ethics committee of potential harassment – we recorded the stage of participation in the trial for each individual. The rationale for this approach was that different phases of the research might present new issues for participants, and that the meaning of the research might also vary along the continuum of involvement. Participants were interviewed from 5 weeks post recruitment to the trial, through to the time of completing a final 12-month questionnaire. Nevertheless, retrospective analysis of the data set did not reveal notable thematic differences across the participants' stage of participation. Appendix 5 contains a consolidated standards of reporting trials (CONSORT) checklist for the process evaluation and an adapted flow chart of participant recruitment.

Role of the qualitative researcher in the trial team: ethnography

The ethnographer worked closely with the trial team on a daily basis. This proximity had clear advantages with regard to accessing materials, and attending/observing everyday events in the construction and deployment of the trial. All members of the trial team were accommodating of requests for interviews and recorded meetings; however, it took time for both parties to understand the role of the other. For the trial team it was initially disconcerting having their activities routinely observed and recorded, and for the ethnographer it was initially difficult to decide what was useful data from the vast quantity of information collected.

The status of the process evaluation as an integral component of the LIFELAX trial ensured that all team members gave their formal consent to participate in the ethnography, and, in this regard, access to some forms of data was assured. Formal consent was obtained from all individuals attending audio-recorded meetings, and additional consent was obtained for interview data. Formal and informal consent was obtained before reporting data contained in field notes.

The ethnographer was offered a significant level of disclosure and cooperation by the trial manager and the dietitian tasked with developing the training packages. In addition to offering personal friendship, the trial manager became a key informant and confidant during the conduct of the trial, facilitating the ethnographer's understanding of the activities at hand. Both contacts facilitated initial attempts to understand and map the terminology of the RCT, the intricacies of its design, including the basis of the interventions, and, perhaps most usefully, the broader administrative and bureaucratic networks in which the RCT was embedded. Moreover, the ethnographer was occasionally given small tasks within the RCT. This role, however small, facilitated the ethnographer's integration with other trial team members.

Through observation, participation and personal contacts the ethnographer was therefore able to map interactions that would have been problematic topics within an interview setting.

Analysis

The process evaluation used a combination of qualitative research techniques. In broad terms, we followed the precepts of Glaser and Strauss's model[138] of constant comparison to develop first-order analyses of the data. The NPM[137] was applied to emergent categories in a cyclical process, whereby the model's constructs were partially redefined to fit the nature of the data. Because of the relatively large body of data collected we used NVIVO 7 collation and management software. Analysis occurred through application of the model's four constructs, as illustrated in *Table 6*.

TABLE 6 *The four constructs of the NPM*

Interactional workability
How a complex intervention is practically enacted by the people using it
Q. *How does the work get done*?
(e.g. In LIFELAX, how did the trial team practically implement the trial? What did practice staff report regarding implementation of training materials and contact with participants?)
Skill-set workability
The distribution and conduct of work associated with a complex intervention in a division of labour
Q. How is the work distributed?
(e.g. In LIFELAX, which groups of NHS staff were targeted by the training interventions, and how did they configure the work alongside ongoing responsibilities?)
Relational integration
How knowledge and work about a complex intervention is mediated and understood within networks
Q. *How is the work understood by the people doing it*?
(e.g. In LIFELAX, how do the trial team reconcile differences in the implementation of RM&G guidance across PCT sites? How do practice nurses make sense of the training sessions based on BCC?)
Contextual integration
The incorporation of a complex intervention within an organisational domain
Q. How is the work supported?
(e.g. In LIFELAX, what work needs to be performed in order to implement an RCT in primary care practices?)
RM&G, Research Management and Governance.

Initial field work consisted of mapping both the stakeholders and structures of the system, from which a sample of both intervention situations and interviewees were chosen. It was particularly important to observe routine and problematic applications of each arm of the trial, especially the negotiations over treatment modalities and how the boundaries between these were agreed.

Local documentary materials (e.g. protocols, correspondence, minutes of meetings, notices, leaflets, entries in newsletters), in which the trial was explained to professionals and subjects, were analysed for comparison, with themes emergent in the interview data and with the wider literature concerning HTA as a discrete field.

Due to recruitment difficulties in both the LIFELAX trial and process evaluation, it is not possible to claim that we finished data collection at a point of 'category saturation' in thematic analysis (i.e. no new forms of data were emerging) for all of the categories of contributors (such as senior partners and practice managers). Nevertheless, data collected across the larger categories of 'primary health-care staff' and 'participants' was thematically consistent bar several 'deviant cases', as described in Chapter 7.

The nature of the process evaluation posed important ethical and practical problems. It was particularly important that the contributors at every level felt safe to report on difficulties and disagreements about the focus, design and implementation of the RCT. At the outset, therefore, we needed to be able to promise the contributors that 'data' would be treated in a way that was 'non-attributable', and that it would be protected in the same way that we would wish to protect, for example patients in a study using these techniques. To ensure that this was accomplished, we do not identify individuals or specific PCTs or practice sites in this report or in any other presentation or publication that was made as a result of this study. Our previous experience in such work has demonstrated to us that this is the only way to ensure openness and candour on the part of participants, and so effectively achieve the objectives of the study.

Chapter 3
Development of the interventions

In this chapter we will look at the evidence that supported the design of the two diet and lifestyle intervention arms in LIFELAX. In essence, the lifestyle and nutritional guidelines that underpinned both the standardised and personalised intervention arms were the same and it was in the style and mode of delivery that the arms varied.

In LIFELAX, the model we adopted was one in which health-care professionals (usually practice nurses) were trained to deliver the diet and lifestyle interventions. The models of delivery of both the standardised and personalised interventions were informed both by theories of behaviour change and by considerations of the practicalities of implementing these interventions in the primary care settings. We invested a great deal of time, effort and resources in the intervention development phase, working closely with practice staff and patients in two local surgeries to inform the design of interventions that health-care professionals could deliver and wanted to deliver. During this pilot phase, patients were consulted and this feedback was used to inform the content, language and layout of the information booklets we developed.

Not all of the findings of the studies on behaviour change that we used to inform the intervention were appropriate for both arms. We were seeking to develop two notionally different interventions. One of the arms (standardised diet and lifestyle advice) needed to sit firmly within the current nursing model in the UK[84] and be suitable for delivery within a routine appointment time (10 minutes). The other arm (personalised diet and lifestyle advice) would be informed by techniques and skills that had been shown to be effective in interventions of behaviour change in similar topic areas and similar populations to ours. (The contents of both the standardised and personalised manuals, along with the information leaflets, can be found in Appendix 3. Copies of the manuals and patient literature are available for purchase from the LIFELAX team.)

Motivating patients and facilitating health behaviour change are key roles for health-care professionals; it was therefore important for the diet and lifestyle interventions to map on to these aspects of routine practice. The standardised intervention arm followed the Pendleton *et al.*[84] model. The Pendleton model has two main components. The first component is to do with the nature of the consultation – the aim is to produce an effective consultation between practitioner and patient in which they work together, both to define the problem and decide the solution. The second component of the model is to do with the teaching method used during the consultation – Pendleton *et al.*[84] describe a teaching method by which both the teacher and the learner enable the learner to build on his/her strengths and ability to be effective.

In the consultation there are a number of tasks:

- Understanding the problem:
  - the nature and history of the problem and its effects.
- Understanding the patient:
  - look at the problem from the patient's perspective.
- Sharing the understanding:
  - consider other problems
  - consider options and implications.
- Sharing decision and responsibility:
  - enable the patient to manage the problem
  - choose the most appropriate course of action
  - practitioner and patient both have responsibility
  - agree goals.

Maintaining the relationship

It is by understanding the problem and the patient, and by sharing this understanding, that the health-care professional will be working towards fulfilling the aim of the first component one of the model: effective consultation. It is by using an educational style that allows the patient to build upon their existing abilities to manage the problem, rather than by telling the patient what to do, that the spirit of the Pendleton approach is upheld. The standardised intervention focused

on enabling the practitioners to have the most up-to-date knowledge and information on constipation. One general PIL was developed for the standardised arm of the trial. The aim was to enable the practitioner to understand what constipation meant to their patient and to explore the options for management. The practitioner had 10 minutes in which to see patients and to set goals for changes to their diet and lifestyle.

The personalised intervention arm drew on a range of models of behaviour change. It is the development of the resources, training and materials for the personalised intervention arm that is the main focus of the remainder of this chapter.

Theories and models of behaviour change

There is a wide range of conceptual models of behaviour change, such as Bandura's Social Cognitive Learning Theory, Becker's Health Belief Model, Azjen and Fishbein's Theory of Reasoned Action, Prochaska and DiClemente's Stages of Change Theory (discussed in greater depth in the section entitled Motivational interviewing, below) that can be applied to the primary health-care setting.[139–141] When designing the interventions for LIFELAX we reviewed evidence from interventions, theories, techniques and counselling styles that had been used to encourage individual (patient) behaviour change. From the outset we were minded to produce interventions that would use techniques and skills already familiar to health-care professionals and that would be easily communicable to them so as to reduce any potential barriers and patient dissatisfaction that are documented to arise from poor communication.[142]

Interventions for behaviour change in healthy eating

From a review of literature indexed in MEDLINE, Web of Science and CSA Illumina on the effectiveness of interventions to promote healthy eating in the general population, it was apparent that there was a number of specific characteristics common to the successful interventions.[140] According to the review, any intervention, whether the focus was on diet alone or on diet and exercise, should be based on a model of behaviour change (i.e. it should be theory and goal driven) rather than simply on the provision of information. Successful interventions tended to be the ones that emphasised personal contact and were related to specific behavioural change strategies. Tailoring the intervention to the patient by using individualised personalised materials or using trained personnel to deliver a case by case intervention was also shown to be beneficial. Opening a dialogue between the health-care professional and patient that allowed for feedback on changes in behaviour (i.e. multiple contacts over an extended time period) was also found to be advantageous.

Physical activity interventions in primary care

In a review of primary prevention and secondary prevention interventions (12 and 24 studies, respectively),[143] the authors identified several components of an intervention to promote physical activity that are likely to improve success (some of which had also been identified as being associated with successful interventions for dietary change), these include:

1. using behavioural approaches (individualised goal setting and problem-solving, self-monitoring, feedback and reinforcement)
2. supervised exercise
3. provision of exercise equipment.

The concept of 'self-efficacy' was highlighted and shown to be closely linked to a stage of self-change in physical activity. Individuals at the different stages of preparedness to change have different 'degrees of exercise specific self-efficacy'.[144] Individually tailored reports and self-help manuals matched to the patient's stage of motivational readiness to start physical activity were found to increase physical activity significantly more than standard self-help materials.[145] A brief negotiation intervention, based on motivational interviewing, was found to be more effective than attempts to persuade or coerce.[146]

Interventions for elderly people living in the community

The decision to exclude non-community dwelling older adults from the LIFELAX study had been taken at the design stage as it was felt in residential

care people would have less control over what they ate, and therefore that there would be less opportunity for them to make lifestyle changes. As elderly people living alone in the community account for 80% of the lowest single household income groups[147] it was important that the diet and lifestyle changes promoted by the interventions were not costly to the individual. There is a paucity of literature on interventions that are focused on community-based nutrition. From a review of 23 such studies, none of which was from the UK (21 from the USA, one in Australia and one in France), we concluded that there was limited evidence for the effectiveness of healthy eating interventions in the elderly.[147] However, the review did find that the strategies of individual feedback and goal-setting highlighted previously[142] were beneficial and were associated with a positive intervention.[147] The review restated the fact that the elderly community dwelling population is a heterogeneous group and that more research is required to identify suitable approaches at different age groups, social class and health status.[147]

Primary care as a setting

Promotion of behaviour change in general practice

General practitioners have very little time with a patient to embark upon any programme of individual behaviour change. In the UK, people see a GP on average five times a year for an average consultation time of 9.4 minutes, which equates to 47 minutes of contact time per year per patient.[148] This lack of contact time with the GP and the belief that the practice nurse was more likely to deal with patients with constipation added strength to the argument that it should be members of the nursing staff who were trained to deliver the intervention. Other studies[149–151] have found that, although patients report high levels of satisfaction with both GP and nurse encounters, patients report greater levels of satisfaction with nurse consultation than with GP consultations. These studies found that there was no significant difference in other health outcomes and most found that consultations with nurses tended to be slightly longer than with GPs, that nurses gave more information to patients and that they offered more advice on self-care and disease self-management. These findings reinforced the choice of the practice nurse as the lead in delivering the diet and lifestyle interventions.

Based upon the knowledge that health-care professionals may not give advice during a consultation unless they understand and believe the information themselves,[152] we decided to involve health-care professionals in the planning of the interventions and the production of the materials used.

There is good evidence for the use of counselling-style interventions in promoting dietary change in primary care.[153] Face-to-face dietary counselling either in small groups (two to three members) or individual sessions of 5 minutes (or less), which provided self-help material and interactive health communications, were viewed as being 'promising'.[153] This review found that effective interventions are those that combine nutrition education with behaviour-orientated counselling to provide patients with the skills, motivation and support they require to make lifestyle adjustments. Examples include:

- teaching self-monitoring
- training individuals to overcome common barriers to eating a healthy diet
- goal-setting
- shopping and food preparation guidance
- intratreatment social support.

The above recommendations were incorporated into the interventions.

A systematic review of 37 trials (10 dietary and six exercise behaviours) concluded that primary care-based health programmes do have a modest and variable effect on lifestyle change.[154] From this review, it was, however, difficult to draw any meaningful conclusions from the dietary trials as the interventions varied widely. Exercise interventions showed promising evidence of their effectiveness.

Though the importance of nutrition is not disputed by primary health-care professionals, there are a number of barriers that are known to restrict their provision of nutritional counselling. These include lack of time, lack of training in behaviour change,[155] a belief that patients will not follow their advice, a lack of reimbursement for counselling and inadequate teaching materials.[156] As described in Chapter 4, despite our best efforts to address all of these in the interventions we designed and the support we provided, these barriers are highly resistant to change.

The practitioner, patient and concordance with regimens

Only about one-half of patients comply with long-term drug regimens and even fewer comply with changes in lifestyle, especially when an advice giving approach is used.[157] The dominant paternalistic style of a physician (or other health-care professional) giving their patient advice is often not a suitable model for chronic disease management or health promotion. The model of a 'meeting between experts', where both the patient and health-care professional are considered to be experts on the patient's problem, and changes are negotiated to enhance the patient's well-being, is a more successful approach.[157] Motivational interviewing is one such negotiation-based strategy; it is very much a 'client'-centred approach (discussed below) and enables health-care professionals to share information and offer suggestions.

Delivery methods for behaviour change

With the absence of standardised definitions of the techniques included in behaviour change interventions, it is difficult to both replicate effective interventions and identify the techniques contributing to effectiveness across interventions.[158] At the outset we need to make it clear that the approaches or methods described below are not mutually exclusive. Many of the techniques and practitioner skills are common to several or all of the techniques, and are those shown to be effective in previous studies of interventions designed to promote individual behaviour change in diet, physical activity, etc. as described above. They also have a theoretical underpinning in models and theories of behaviour change. LIFELAX made use of a combination of the approaches outlined below to develop the most practical approach to the development and delivery of personalised diet and lifestyle advice by nurses in the primary care environment.

Tailored information

There are two main forms of health communication – targeted generic and tailored communications.[159] 'Targeted generic' information is defined as material intended to reach a specific subgroup of the general population, based on one or more demographic characteristics, while tailored information is designed to reach one individual, and is derived from individual assessment and is unique to that individual.

Generic information is less costly to produce than tailored information, although there is evidence of the success of the use of tailored information disseminated using a variety of communication methods including the telephone, audio, video, internet or other electronic media.[159] A review of eight tailored/generic comparisons found evidence that tailored personalised communications were more effective than generic, non-tailored communications;[160] therefore, in the personalised arm of LIFELAX all communications were suitably personalised (targeted to the individual).

Motivational interviewing

While motivational interviewing holds 'substantial promise for health behaviour change', is patient centred, can be tailored to the patients degree for readiness of change and is an effective means for working with patients who are ambivalent or not ready for change, it should be added as a note of caution that few controlled studies measuring the efficacy of motivational interviewing exist, and little is known about how to structure sessions.[161]

Motivational interviewing is 'a directive, client centred counselling style for eliciting behaviour change by helping clients to explore and resolve ambivalence'.[162] Motivational interviewing has four principles:[163]

1. expressing empathy
2. developing discrepancy
3. rolling with resistance
4. supporting self-efficacy.

Table 7 shows the characteristics of what is and what is not a characteristic of motivational interviewing.

Motivational interviewing is not defined as a technique per se but rather by 'its spirit as a facilitative style for interpersonal relationship(s)'.[162] This 'spirit' involves collaboration between health-care professional and patient. The health-care professional elicits the motivation to change from the patient, through drawing on their patient's own perceptions, goals and values, while the responsibility for change remains with the patient.[163] The focus of the motivational interview is to examine and resolve ambivalence, defined as a key obstacle to change, in a patient-centred and directive manner.[162]

Although not explicitly based on any specific theory of behaviour change, motivational

TABLE 7 *The characteristics of motivational interviewing*

Motivational interviewing	**Opposite to motivational interviewing**
Collaboration	Confrontation
Partnership conducive to change	*Ignoring patient's perspective*
Evocation	Education
Intrinsic motivation to change is drawn from patient's own goals	*Aim of the practitioner is to educate the patient for change to occur*
Autonomy	Authority
Patient-led self-direction	*Practitioner tells patient what to do*
Adapted from Miller and Rollnick.[163]	

interviewing has been linked with the Transtheoretical Model of Change,[164] which assists by 'providing a framework for understanding the change process itself', whereas motivational interviewing provides 'a means of facilitating this change'.[161] The combination of motivational interviewing with the Transtheoretical Model has been described as an 'optimal patient encounter'.[142]

Because the notion of a readiness to change is important in all motivational interviewing approaches, including 'brief motivational interviewing', it is necessary to have a working understanding of the Transtheoretical Model (*Figure 1*).[165]

Debate as to the merits of the Transtheoretical Model as a predictive or descriptive model is beyond the scope of this report; suffice to say that this is a model with which health-care professionals are familiar, and it provides a useful lexicon to describe people as they undergo a behaviour change intervention. The rationale behind this model is that behaviour change does not happen in one step. People tend to progress through different stages on their way to successful behaviour change. People also progress through the stages at different rates. Expecting behaviour change from someone who is still in the 'pre-contemplation' stage is unlikely because, when in this stage, the individual is not ready to change. Decisions as to when to move through the stages (i.e. when a stage is complete) must be made by the patient, as opposed to being imposed by the health-care professional. In each of the stages there is a different set of issues and tasks that relate to changing behaviour. The health-care professional can use different tools and techniques at each stage.

The focus of traditional medical consultations regarding behaviour change is 'advice giving'. As discussed above, this paternalistic approach is not always the most effective mechanism and may be met with resistance and disagreement between patient and practitioner.[166] In behaviour change interventions, ambivalence to change is an often encountered problem. Ambivalence to change can be characterised as a conflict between two courses of action (patient and counsellor). It is difficult to resolve as each party has benefits and costs associated with the behaviour change.[166] This is particularly true when a directional (e.g. advice giving) approach, with unequal partners, is adopted, rather than a negotiated strategy. Motivational interviewing, although it uses a non-directive counselling approach, is a negotiated approach and does focus explicitly on ambivalence and the resolution of it.[167] The practitioner can positively or negatively influence their patient's resistance to change and the outcome of the consultation. Negotiations in which the patient expresses his/her perceptions of the costs and benefits of change have been shown to promote the patient's motivation to change.[166] Behaviour change interventions that tailor advice to the patient's readiness to change should ensure closer agreement between patient and practitioner, encounter less resistance and improve the effectiveness of the intervention.[166] The most successful use of motivational interviewing is when the patient is given individual, personalised feedback.[168]

While we knew that some of the practice staff involved in the LIFELAX intervention delivery would have a specific interest or experience in constipation or GI conditions, there was good evidence to suggest that motivational interviewing could also be successfully used by health-care professionals that were non-specialist in a specific field.[169]

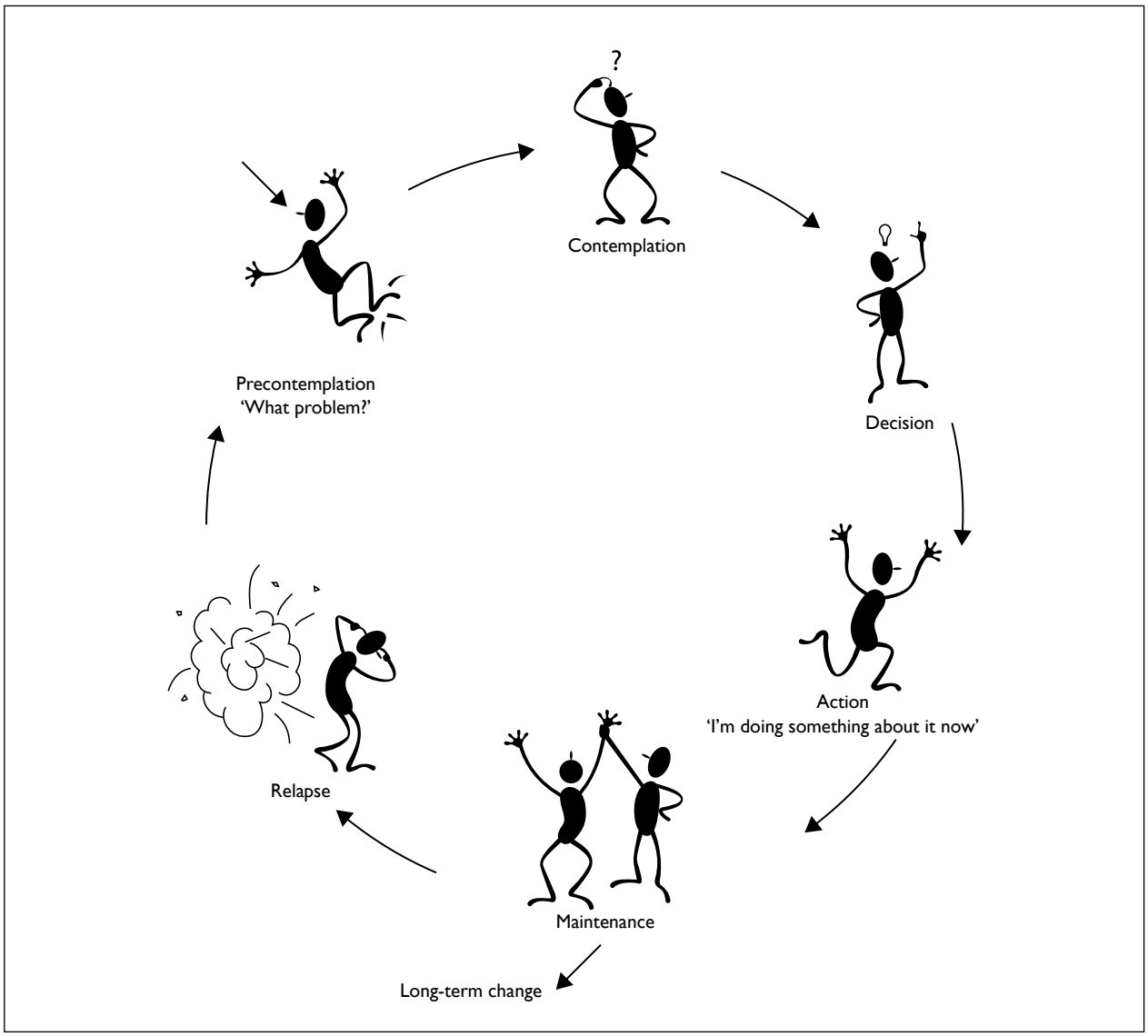


FIGURE 1 *The Transtheoretical Model. Adapted from Prochaska and DiClemente.*[165]

Despite these theoretical benefits of motivational interviewing, we were aware that the most limiting factor in using motivational interviewing in a medical or public health setting is time,[170] in particular the length of time available in the 'normal' appointment slot for either GPs or practice nurses. For LIFELAX, therefore, we recognised that a briefer format of motivational interviewing would be required. Within the time constraints of the normal encounter with a practice nurse, we felt that there might not be sufficient time to fully explore the patient's ambivalence. We were also aware that asking health-care professionals to adopt the LIFELAX intervention protocols may require some adjustment from the traditional prescriptive methods of patient education (i.e. provision of advice) to becoming more facilitative and collaborative.[170] Health-care professionals delivering the interventions in the trial would be required to leave their traditional 'expert' role and allow the patient to become the expert.[167]

Brief motivational interviewing

Brief motivational interviewing techniques have been used with success in brief interventions in primary care in a range of topics, for example perinatal drug use,[171] to improve dietary adherence in adolescents[172] and psychiatric patients' attitudes to their care, motivation to change, compliance and outcome.[173] There are a number of key elements that characterise a successful brief intervention and these should be apparent to anyone observing such a consultation.

These elements are represented by the acronym FRAMES.[174]

- *Feedback* Systematic assessment and feedback of individual findings.
- *Responsibility* Emphasising the individual's personal responsibility for change, that this change is a free choice and a personal decision
- *Advice* Advice giving consists of two negative factors: first, it provides the patient with information (usually using tactics of fear induction), and, second, it uses persuasion (why a patient should do what you tell them).
- *Menu* The variety of ways in which change could be accomplished.
- *Empathy* Style of counselling.
- *Self-efficacy* Intervention should contain elements to strengthen the individual's self-efficacy.

Despite 'advice' being a key element, it is important to recognise that 'brief motivational interviewing' consultations are not in the traditional advice-giving mould; advice is not given without the patient's permission, and when advice is given it needs to be accompanied by encouragement for patients to make their own decisions.[161]

Brief motivational interviewing was developed for use in a medical setting, where most patients do not enter in a state of readiness to change.[175]

An implication of the Transtheoretical Model is that, before attempting to give people the skills and resources needed to change their behaviour, it may be more effective to assess their readiness to change. A person's preparedness to change can be assessed accurately by the use of a questionnaire;[176] however, this is likely to prove to be impractical in a routine clinical setting. Other useful tools to assess readiness to change, including an agenda setting chart (*Figure 2*), a 'pros and cons' chart (*Figure 3*) and a readiness-to-change ruler (*Figure 4*), have also been developed.[177] In LIFELAX we produced an agenda-setting chart that allowed patients to address constipation-specific factors (known to impact on bowel health), such as exercise, diet and fluid, as well as three open options where the patient could identify their own priority areas. In the intervention, patients were encouraged to identify their own priority items and set achievable goals when they were ready (*Figure 5*).[178] We understood that patients might well have had a rigid mental picture as to the consultation that they should expect when they underwent the intervention. We were aware that changing the consultation process and associated behaviours might not be easy; however, we felt that the simplicity of the agenda-setting chart, and its ability to help patients express choice and take the lead in target-setting, would make it a useful instrument.[178]

In order for behaviour to change, a person needs be motivated to change their behaviour and feel confident to do so. Motivation can be defined as the individual's expectations of the costs and benefits of change, whereas confidence may be described as their ability to master the demands of assistance. Bandura's Self-Efficacy Model and the distinction between outcome and efficacy expectation provide a theoretical framework to use motivation and confidence.[179] Exploring the importance of changing a behaviour with the patient is an important exercise. For this exploration, a 'pros and cons' chart was developed (see *Figure 3*). Using this chart it is possible to explore and record the positives of making a behaviour change and staying the same. Below is a worked example.

Confidence to change can be assessed simply by asking two questions:[180]

1. 'If on a scale of 1–10, where 1 is not at all motivated to eat more fruit and 10 is 100% motivated to eat more fruit, what number would you give yourself at the moment?'
2. 'If you were to decide to eat more fruit now, how confident are you that you would succeed? If, on a scale of 1–10, 1 means that you are not at all confident and 10 means you are totally confident that you could eat more fruit, what number would you give yourself now?'

After the topic (eating more fruit) had been raised, the aim of the next stage would be to identify arguments for change (motivation) and practical steps to make the change (confidence); this could be done through scaling questions

- First, by asking the patient why they scored as they did rather than a lower number:
  - 'Why have you given yourself a score of 6 and not 1?'
- Second, by asking the patient what would need to be in place for them to move to a higher number:
  - 'What would have to happen for your motivation score to move up from 6–9?' 'How could your confidence score move up from 5–8 or even 9?'

FIGURE 2 *LIFELAX agenda setting chart.*

	Staying the same	Changing
Pros	I wouldn't have to change a thing	I could do without my laxatives
Cons	I'd still need my laxatives every day	I would have to change my diet

FIGURE 3 *LIFELAX pros and cons chart.*

This information would then be incorporated into the 'setting aims and plans' sheet (*Figure 5*) as part of the 'contract' between the patient and health-care professional during the LIFELAX personalised intervention counter between the patient and health-care professional. Patients would take a copy of this away and a copy would also be retained in the practice for future reference in terms of follow-up telephone calls and follow-up visits.

Counselling

Counselling is defined as a 'cooperative mode of interaction between the patient and primary care

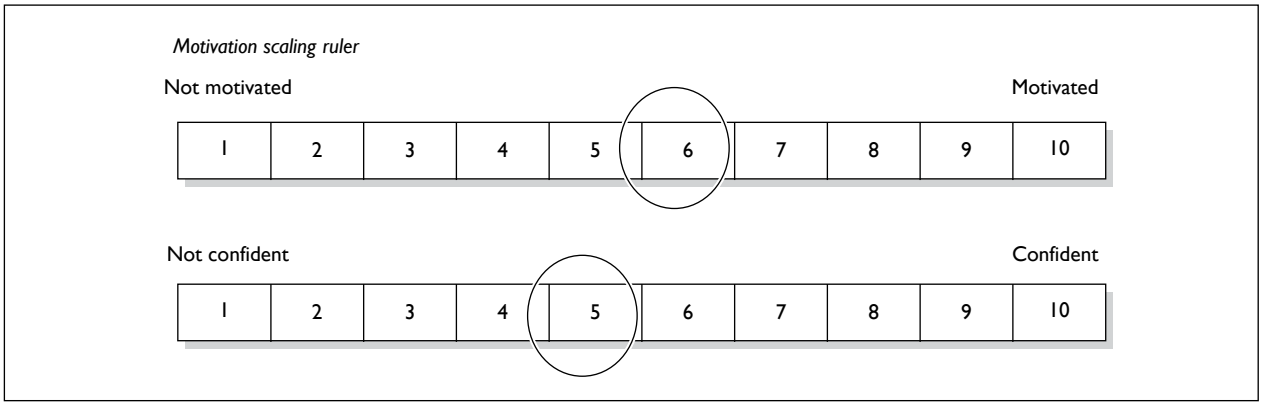


FIGURE 4 *Scaling tools.*

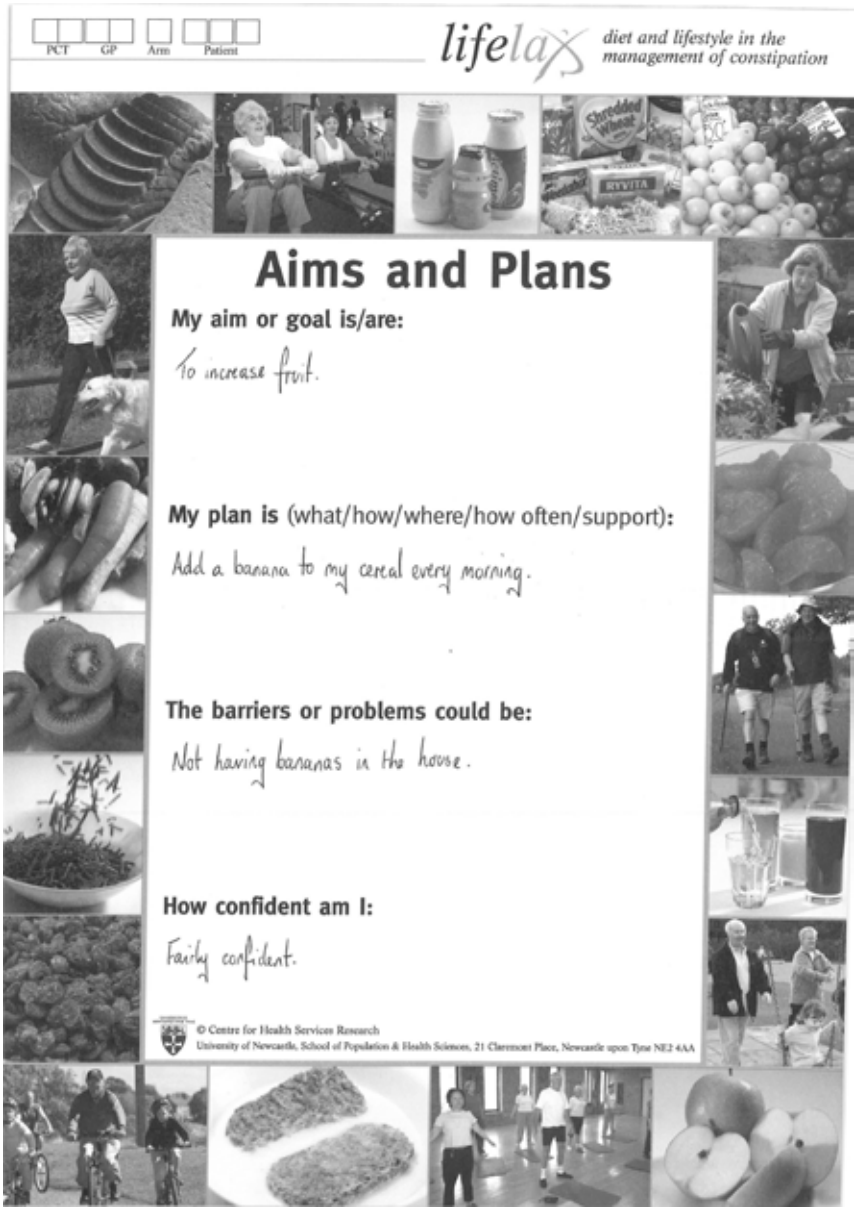


FIGURE 5 *Setting aims and plans.*

physician or related health-care staff members to assist patients in adopting behaviours associated with improved health outcomes'.[181] Improved behavioural outcomes in dietary counselling are thought to be associated with a number of factors, including the use of dietary assessment, enlisting family involvement, providing social support, using group counselling, emphasising food interaction (tasting, testing and cooking), encouraging goal setting and using advice appropriate to the patient group.[182]

In a review of 21 studies, focusing on the counselling effect on changes in fat, fruit, vegetable and fibre intake, higher-intensity interventions, (more than one 30-minute contact) were found to be more effective than lower-intensity interventions.[181] Counselling interventions using self-help material and interactive communication alongside brief provider advice seemed to produce medium changes. Elsewhere, behavioural counselling to increase fruit and vegetables consumption have also been shown to be effective.[183] The PILs were designed to enable respondents to think about their current practice and to compare this with recommendations. For example, the PIL on 'Fluid and constipation' contained a fluid counter, the 'Fibre and constipation' PIL contained a fibre counter, and the 'Activity and constipation' PIL, an activity counter.

Behaviour change counselling

In addition to the principles of (brief) motivational interviewing, and the models and theories that underpin (brief) motivational interviewing (the Transtheoretical Model, and Bandura's Self-Efficacy model), the personalised diet and lifestyle arm of LIFELAX also drew heavily on the BCC model. BCC[184] is a set of consulting strategies derived from the patient-centred method,[185] health behaviour change[184] and motivational interviewing.[163] See *Table 8* for a summary of the characteristics of BCC. As we described above, motivational interviewing is a directive, patient-centred counselling style for increasing intrinsic motivation by helping patients explore and resolve ambivalence. Being 'patient-centred' involves a number of factors:

- It is an active process that involves both patient and practitioner.
- There is a core partnership between patient and practitioner.
- It is not directional advice giving.
- Careful listening – listening to the patient to learn from them.
- The patient has greater control in decision-making.
- The practitioner and the patient reach joint decisions together.

Behaviour change counselling, like motivational interviewing and brief motivational interviewing, has been developed for brief health-care consultations to help the individual talk through the 'why' and 'how' of change. The practitioner's main task is to understand how the person is feeling and his/her plans for change.[40]

TABLE 8 *The characteristics of BCC*

Goals	Establish rapport, identify goals, exchange information
	Choose strategies/goals based on individual's readiness
	Build on motivation for change
Style	Practitioner – patient both active
	Seldom confrontational
	Use of an empathic style, information is exchanged
Skills	Ask open-ended questions
	Summaries
	Ask permission
	Encourage patient choice and responsibility
	Provide advice
	Reflective listening

Adapted from Rollnick *et al.*[184]

As in motivational interviewing and brief motivational interviewing, establishing rapport is an essential component of BCC consultations. Once rapport is established, two-way information exchange tends to occur more readily. Establishing the patient's readiness for change and what behaviour to focus on are also parts of the BCC approach. Establishing and agreeing goals and strategies for behaviour change should involve the patient setting realistic aims and plans that can be achieved. The consultation is an active process that involves both the patient and the practitioner; it should be collaborative, rather than prescriptive, and should be non-confrontational. By the professional asking permission to discuss a topic during a consultation, the patient will not feel it has been forced upon them.

Empathy – which can be defined as: 'the ability to share someone else's feelings or experiences by imagining what it would be like to be in their situation'[186] – is a further core skill of the BCC process. This includes empathic listening, an active listening process, and demonstration that the professional is indeed listening, by replying and reflecting to what the patient has just said. For example:

> *Patient:* 'Being constipated makes me feel lethargic, I can't be bothered doing anything and I am scared of leaving the house.'
>
> *Practitioner:* 'Your constipation makes it difficult for you to be more active – that must be hard.'

The BCC interviewing style is one that 'quiet and curious' – allowing the patient to do more talking, using open-ended questions, rather than closed questions.[184] Empathic listening, reflection and summaries are useful in rapport building and also ensure that aims are understood by both patient and practitioner. The practitioner provides structure to the consultation but decision-making should be shared[184] (*Figure 6* – suggested BCC consultation 'flow') and should be the patient's choice as well as their responsibility. In BCC, as in motivational interviewing, it is vital that practitioners avoid falling into a paternalistic, directional advice-giving trap. Evidence suggests that this generally does not induce behaviour change.[184] When advice needs to be given, a more positive form of advice giving is giving a number of options, with the patient choosing the most suitable one.

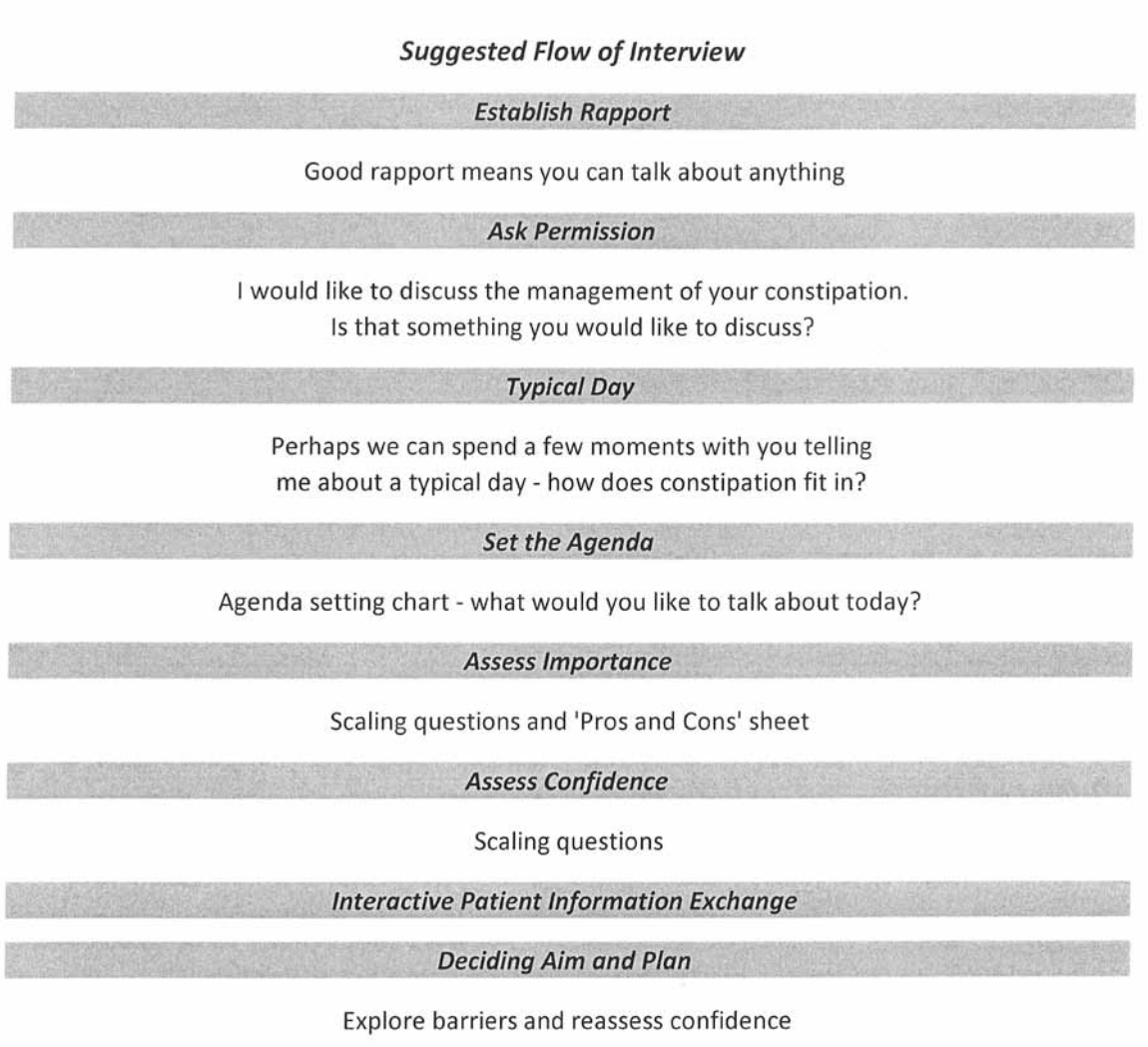


FIGURE 6 *The BCC consultation 'flow'.*

The key principles that underpinned the LIFELAX personalised intervention

- Individualised goal identification.
- Realistic goal setting.
- Practitioner listening to the patient.
- The intervention being directed by the patient.
- Setting and following up the patient's individual goals, using a range of novel tools: the agenda-setting chart, the scaling tools, the 'pros and cons' sheet and the goal-setting sheet.
- Monitoring of patient's progress using specifically developed PILs containing tools, such as a fluid counter, fibre counter, measures of physical activity.
- A user-friendly and accessible practitioners' manual that had all necessary trial information, and set out clearly and concisely what was required in the intervention.
- Training materials and resources.

From visiting practices and speaking to practitioners, the study team established that there was a scarcity of independent constipation, diet and lifestyle PILs, with the majority being produced by drug companies and laxative producers. A comprehensive suite of materials and resources was developed to enhance the LIFELAX interventions. We worked closely with patients and health-care professionals to develop many of the tools and the information materials needed. For example, we used cognitive interviewing techniques to test the acceptability and comprehensibility of the PILs (from text to pictures) and thereby to ensure their relevance and acceptability to the target audience.[119]

High-quality training and reference manuals for health-care professionals were produced for both the standardised and personalised diet and lifestyle intervention arms. These contained the entire set of information (see Chapter 1, Impact of diet and lifestyle on constipation) that health-care professionals would need about constipation and bowel health, as well as full details of the delivery style and techniques for the appropriate arm.

Training of practice staff was envisaged to take place over a number of visits (one to two) for the standardised arm and (two to three) for the personalised arm. The training sessions were conducted by the project dietitian and nutritionist. As we were aware that we might be asking practitioners to change their consulting behaviour, this training drew heavily on the behaviour change techniques we were passing on for LIFELAX. However, after much discussion within the team it was agreed that there would be no formal assessment of the any health-care professional's preparedness to change their own consulting behaviour.

The time available to train health-care professionals in the intervention techniques was always an issue in this trial; however, the importance of training cannot be over emphasised.[167] We needed to be flexible and to tailor our training to fit in with the practice schedule. There is evidence that training based upon two or three 1- to 1.5-hour training sessions and role play demonstrations is successful.[177] We were told by the practices involved in developing the interventions that practice nurses would not readily enter into or enjoy role play, especially if senior colleagues were to be involved or observing. As a result of this, we elected to produce training DVDs in place of the role play. Evidence suggests, too, that outside of the training sessions few of the health-care professionals were willing to practice the training and techniques.[177] For this reason, we felt that the DVD would serve as a useful resource and *aide-memoire*.

Our experiences of practice training varied from practices that set aside the majority of a day for training to ones that required us to fit in with lunch breaks. Having project staff (a research dietitian) that were sympathetic to and understood the dynamics of working in a primary care environment was seen as an advantage.

We felt it important that staff should have a positive experience from the training, and worked to create sessions that were informative, interesting and with clear useable learning outcomes. We felt that our training DVD helped to avoid the embarrassment of role play and the unfeasibility of offering staff 'refresher' courses.

Novel ways for engaging practice staff and assessing their knowledge of the condition were used, for example we used the quiz show formats of *'Who Wants to Be a Millionaire'* and *'The Weakest Link'* rather than a more formal assessment or lecture. A lecture would imply they may not know how to deal with constipation, whereas the quiz format was a two-way process that facilitated discussions and information exchanges.

Summary

In designing both the standardised and personalised diet and lifestyle interventions for LIFELAX there were a number of theoretical models that we could have potentially chosen on which to base our materials, methods and resources. The standardised approach made use of the existing nursing model in use in primary care as the basis for those appointments. For the personalised intervention arm, we reviewed a number of trials that had successfully used a number of different models and techniques to deliver behaviour change with respect to diet, physical activity and other aspects of lifestyle. We drew on the recommendations from those papers and from other practising health-care professionals to produce training, training materials and literature, the likes of which were not otherwise available to practitioners in the UK.

Copies of the resource packs, PILs and training DVD are available for purchase from the central trial team.

Chapter 4
Implementation of the trial

Introduction

In this chapter we will describe the challenges encountered during the implementation of LIFELAX. These challenges arose both with the recruitment of practices and of patients. The planned recruitment model described in Chapter 2 (which formed the original study protocol) and the account of the reality presented here differ widely. Various reasons for the challenges will be documented in this chapter and the embedded Process Evaluation Study (see Chapter 6) offers a further interpretation on this account.

In summary, some 1114 practices in total were approached and invited to participate. Of these, 44 (just under 4% – 13 short of our target of 57) agreed to participate and were randomised. However, only 19 practices (43% of those randomised – 33% of the target of 57) recruited participants to the trial; 16 practices withdrew post randomisation and six practices were unable to recruit during the time frame available. *Figure 7* presents the CONSORT diagram for the trial.

A total of 154 participants were recruited to LIFELAX. Initial calculations showed that in order to recruit the required number of participants (approximately 1800) for the trial we would need to recruit 57 GP practices (31 patients per practice on average). This would seem now to be a vast underestimate, given the poor levels of participant uptake we experienced.

Preparation and implementation of the trial protocol

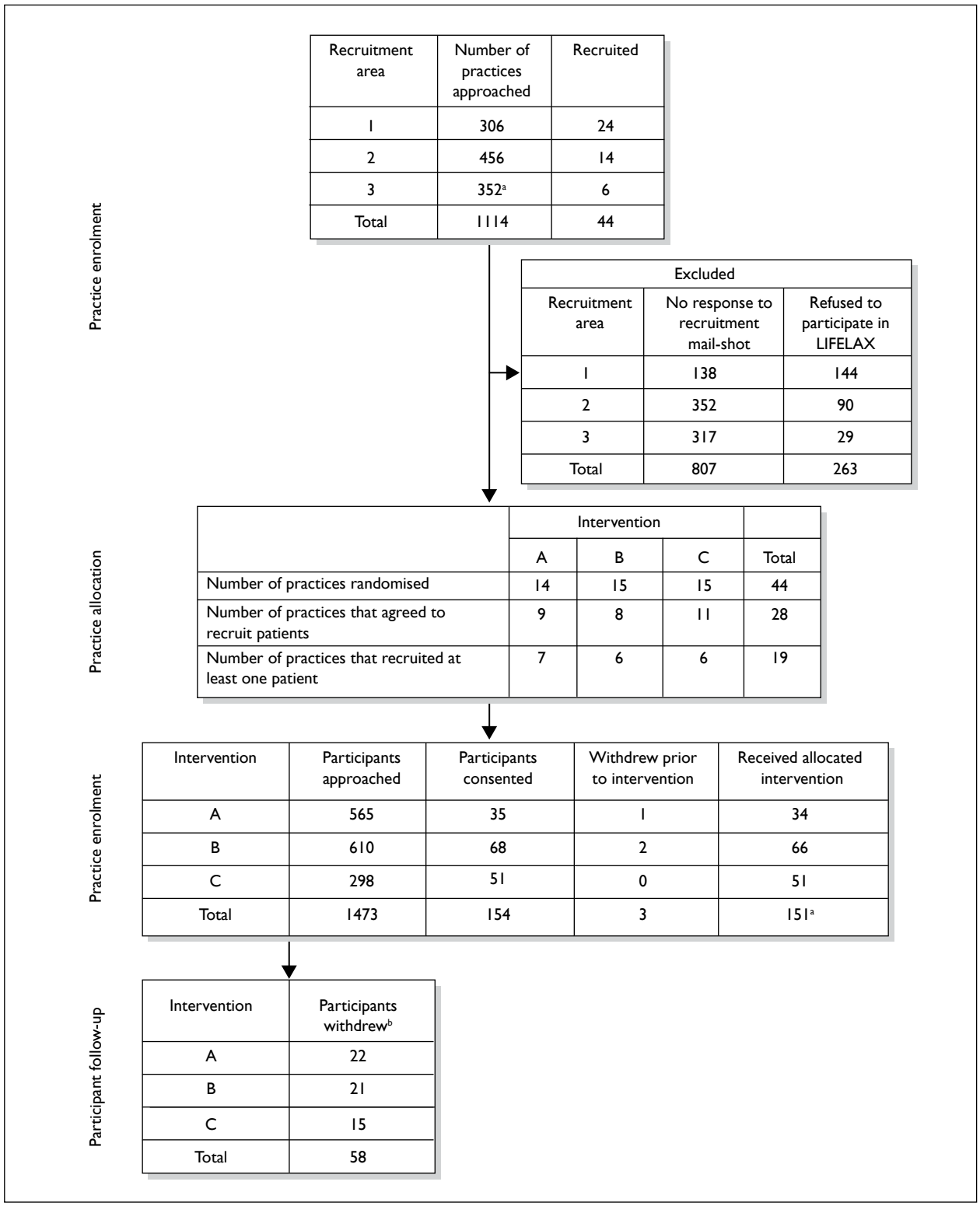
For the findings of clinical trials such as LIFELAX to be generalisable across primary care (i.e. to have external validity), it is important for the amount of research and the proportion of research-active primary care staff, in particular GPs, to increase.[187] Increased participation in primary care trials is a priority in the UK,[188] even although such trials have always been more challenging to researchers than trials in alternative environments, such as the more controlled and more research-orientated secondary care. Added to this 'standard' challenge of primary care research, LIFELAX also coincided with a period of considerable change within the NHS, both in terms of the emergence of a new research governance and ethics framework and the implementation of new GP contracts.

Regulatory approval

Although LIFELAX began after the publication of the EU Clinical Trials Directive, it was prior to the Directive's enactment into UK law. This meant that although the LIFELAX trial appeared to meet the criteria for a clinical trial of an investigative medicinal product (ctIMP) we were able to apply for a Doctors' and Dentists' Exemption (DDX) certificate when obtaining regulatory approval from the Medicines and Healthcare products Regulatory Agency (MHRA). This meant that we did not need to submit a full application for a Clinical Trial Authorisation (CTA) to the MHRA. In common with all other trials at the time, the DDX was issued and was then 'rolled over' into a CTA on 1 May 2004. (With hindsight it would seem that the study could have made the case to the MHRA that the study was a trial of management strategies, rather than specific drugs. However, the general advice we received was that if there was any possibility of a study being a ctIMP the DDX/clinical trial exemption route should be followed to avoid the additional paperwork associated with obtaining a CTA.)

MREC approval

An overview of the time line for the trial is shown in *Table 9*. The initial ethics application was submitted to the allocated MREC in December 2003, at which time the subsequent approval of the LREC associated with each participating site was required, unless a 'no local investigator' (NLI) status was agreed by the MREC. To reduce the burden on the multiple GPs who were to be recruited to this study, we asked the MREC to consider NLI status for LIFELAX. Unfortunately, NLI status was not granted. The MREC reviewed the application on 22 January 2004. A number



Recruitment area	Number of practices approached	Recruited
1	306	24
2	456	14
3	352[a]	6
Total	1114	44

Excluded		
Recruitment area	No response to recruitment mail-shot	Refused to participate in LIFELAX
1	138	144
2	352	90
3	317	29
Total	807	263

	Intervention			
	A	B	C	Total
Number of practices randomised	14	15	15	44
Number of practices that agreed to recruit patients	9	8	11	28
Number of practices that recruited at least one patient	7	6	6	19

Intervention	Participants approached	Participants consented	Withdrew prior to intervention	Received allocated intervention
A	565	35	1	34
B	610	68	2	66
C	298	51	0	51
Total	1473	154	3	151[a]

Intervention	Participants withdrew[b]
A	22
B	21
C	15
Total	58

FIGURE 7 *LIFELAX CONSORT diagram. a, Although not all consented participants received the allocated intervention they were eligible for a baseline assessment; therefore* n = *154 is used in the analyses of baseline data. b, Not all withdrawals were complete withdrawal from all follow-up assessments; consequently, some participants supplied questionnaire data and not diary data, and some participants agreed to telephone follow-up only.*

of minor changes were requested in the patient information sheets. The MREC delegated authority to their 'lead reviewers' for this application to approve these amendments once they had been received. The formal letter conferring the favourable opinion of the MREC was issued on 12 March 2004.

The LIFELAX trial team had concerns over the burdensome nature of the recruitment protocol submitted to MREC as part of the approval process. This method had been approved by another MREC for the STOOL trial.[19] The approval process for STOOL had taken 15 months, and we were concerned that any deviation in LIFELAX from an already approved method might lead to unnecessary delay. [At this time there were many changes in the research ethics committee (REC) approval process. Many of the recruitment strategies that had been acceptable in earlier studies were deemed to be no longer so. It is in the context of this changing landscape and inconsistencies across RECs that LIFELAX operated.]

LREC approval

As LIFELAX was not able to operate as a NLI study, an extra level of approval was required before recruitment could begin. LRECs treated each general practice recruited into the study as a separate 'site' and required the submission of a separate SSA, accompanied by the CV of the GP taking on the role of principal investigator (PI) for that site, before they would consider that site for approval. The process was made additionally burdensome to GPs as it required that each local PI should apply for an LREC number, complete and sign the relevant form and send it to the appropriate LREC. These requirements created a number of difficulties: many GPs did not have readily available CVs of the type required; many GPs were unfamiliar with the new LREC forms and processes and did not have sufficient time to carry out these tasks; and others felt that they did not wish to be designated as responsible for a study that 'wasn't theirs' and felt that responsibility for the study lay with the research team.

To facilitate this process we designed a short CV template that would allow GPs to provide us with the minimum amount of information required for LREC to carry out the SSA. Having heard anecdotal evidence/horror stories of trials that needed SSAs spending > 7 months on this part of the approval process alone, we made an approach to our MREC, the local COREC manager and the Director of NoReN (the local primary care research network) with an innovative solution.

The COREC guidelines at the time stated that if two or more GP practices had contracted to conduct research collaboratively, whether through a consortium or under the direct management of the PCT, they could be collectively identified as a single site and, in such cases, one of the investigators should be appointed as the PI for the site. Our solution to the local approvals dilemma proposed that NoReN (an inclusive organisation for all north-east general practices, not requiring any practice to 'opt in') should form the consortium with the other recruiting practices in the area, with the clinical director of NoReN (GR, already a coinvestigator on the study) acting as the PI for the purpose of the SSA.[189] This solution was accepted, and notification that the various LRECs had approved LIFELAX to run in the 'Area 1' PCTs came via MREC on 10 November 2004.

Although LIFELAX pioneered this approach, allowing us to speed up the SSA process in the areas covered by NoReN, we were not entirely happy with it as a model outside the NoReN area. Although successful in Cumbria with the CumbReN network (again with the CumbReN director acting as PI for the consortium), there was a concern that should the trial seek to recruit further afield the directors of other GP research networks might not agree to take responsibility as PI for the sites within their network's geographical area. In light of this concern we again approached MREC and asked them to reconsider the 'NLI' status of LIFELAX. At the time of this final approach, the 'NLI' status for trials had ceased to exist. By this time, the LREC approval process required site-specific information (SSI) to be submitted to LREC as part of the local approval process or, in certain circumstances, an SSI exemption could be claimed. After consultation with the local COREC manager and the agreement of the COREC policy officer to support the MREC decision to support the SSI exemption, should it be granted, an approach to MREC for SSI exemption was made in October 2005. We argued that the LIFELAX was a 'low-risk' study, the prescribing of laxatives was in line with normal practice (with no stipulation on class or dosage) and that the behaviour change techniques were often used in routine practice.

After agreeing that LIFELAX was a 'low-risk' study, MREC considered that it could be an 'SSI-exempt' trial (favourable opinion 12 October 2005), which meant that sites no longer needed a GP to act as a PI and that no application to LREC for approval of sites (or consortia thereof) needed to be made.

TABLE 9 *Timeline for the trial*

Month (duration in months)	Activity or comment
June 2003 (1)	Trial manager begins work on LIFELAX (tasks include securing LREC and Trust R&D approval for pilot, preparing the pilot study materials, training in pilot study research methods, and preparation of the documentation and materials needed for the MREC approval application)
	Dietitian appointed and begins work (full time)
July 2003 (2)	Dietitian reduces hours to part-time for personal reasons (work continued on developing the materials for the intervention and dietitian is trained in cognitive interview techniques)
October 2003 (4)	Dietitian returns to full time. Applications for NHS honorary contracts made
November 2003 (5)	LREC approval for pilot study, R&D approval given for pilot
December 2003 (6)	MREC application submitted
March 2004 (9)	Favourable opinion from MREC received; work begins on various LREC applications (i.e. SSAs); ad hoc funding is sought from the DH to 'pay per patient' recruited via the SfS funding stream
April 2004 (10)	Diet and lifestyle leaflets completed for the intervention
May 2004 (11)	Pilot for nurse training begins; PCT/GP meetings attended by trial manager in order to promote LIFELAX and generate interest; ad hoc funding is secured
	Negotiations with COREC re. practices being 'research consortia' with one PI begin
July 2004 (13)	PCT/GP presentations continue; application made to LREC[a] and PCTs for R&D approval
August 2004 (14)	Pilot of nurse training completed; printing of 'packs' and associated intervention materials; training DVD produced
October 2004 (16)	COREC manager supports our attempt to gain SSA exemption
November 2004 (17)	Practice recruitment and staff training begins (area 1); the electronic query is run to identify patients
February 2005 (19)	Follow-up telephone calls begin to practices to discover why there was little interest in the study
March 2005 (20)	Work continues on promoting the trial and looking at ways of making it less burdensome to practices
May 2005 (23)	First training visits to practices arranged (area 1)
June 2005 (24)	Application to MREC made to revise recruitment protocol. Favourable opinion given (20 June 2006); application to revise the ad hoc funding in line with protocol revisions made
July 2005 (25)	Application made to HTA for 22-month extension; six participants consented
August 2005 (26)	10 participants consented
September 2005 (27)	Five participants consented
October 2005 (28)	Three participants consented; SSA exemption given by MREC
November 2005 (29)	Recruitment of practices begins (area 2)
	Four participants consented
December 2005 (30)	Eight participants consented
January 2005 (31)	Eight participants consented
March 2006 (33)	Three participants consented
April 2006 (34)	Eight participants consented
May 2006 (25)	Nine participants consented

TABLE 9 *Timeline for the trial (continued)*

Month (duration in months)	Activity or comment
June 2006 (36)	Approach made to SPPIRe to recruit practices in Scotland; approach to MREC to change the face-to-face baseline assessment to a telephone assessment
	10 participants consented
July 2006 (37)	Favourable opinion from MREC received
	Seven participants consented
August 2006 (38)	Nine participants consented
September 2006 (39)	Three participants consented
October 2006 (40)	One participant consented
November 2006 (41)	Five participants consented
January 2007 (43)	Recruitment in area 3 begins
February 2007 (44)	Two participants consented
March 2007 (45)	Three participants consented
May 2007 (47)	The TSC met and discussed whether there was a viable future for the trial; HTA briefed of the intention to reconvene in October 2007 to make the final decision over a further extension or close down
	Five participants consented
June 2007 (48)	Two participants consented
July 2007 (49)	27 participants consented
August 2007 (50)	Five participants consented
October 2007 (52)	TSC make the close-down decision; recruitment is halted; participants already in the trial are to be followed up as per protocol

DH, Department of Health; HTA, Health Technology Assessment programme; R&D, research and development; SPPIRe, Scottish Practices and Professionals Involved in Research; TSC, trial steering committee.
a NoReN director agrees to act as PI. Any site joining the trial is part of the NoReN research consortium.

PCT selection and R&D approval

Selection and recruitment of PCTs

Primary Care Trusts in north-east England, Yorkshire and Cumbria were initially allocated between the STOOL and the LIFELAX trials. STOOL was allocated some of the more geographically distant Trusts (Cumbria & Yorkshire) as we believed fewer visits were needed to practices to set up that study, as there was no requirement to train practices in the delivery of the stepped-drug-regimen intervention. Training for the diet and lifestyle interventions meant that LIFELAX practices would require many more visits so Trusts closer in proximity to Newcastle upon Tyne were prioritised for that study.

LIFELAX initially sought PCT research and development (R&D) approval from 11 local PCTs (area 1 recruitment) (all PCT names that follow refer to the PCTs in existence at the time of practice recruitment – since that time there have been a number of mergers and a reduction in the overall number of PCTs): Newcastle; Gateshead; South Tyneside; Northumberland; Durham & Chester-le-Street; North Tees; Derwentside; Sedgefield; Craven; Harrogate & Rural District; Scarborough; Whitby & Rydale, and Hambledon & Richmond. Across these 11 PCTs there was a total of 308 practices available to us. We were able to contact only 306 of them for the trial, as two of the practices had been involved in the both the development of the diet and lifestyle interventions and taken part in the STOOL trial qualitative study and we were keen not to overburden their staff and patients. Due to poor GP response rates (14 practices) from this first wave of recruitment, it became necessary for LIFELAX to expand its recruitment area.

In a bid to capitalise on the increased profile of constipation raised by the STOOL trial and to

take advantage of the STOOL trial manager's local knowledge, it was agreed that once it had closed down [the Trial Steering Committee (TSC) agreed the closure of the STOOL Trial in May 2005] LIFELAX would contact those PCTs originally selected for 'STOOL'. Thus, in a second recruitment wave, we approached North Tyneside, Sunderland, Langbaurgh, Durham Dales, Easington, Hartlepool, Middlesbrough, Darlington, East Yorkshire, Yorkshire Wolds and Coast, West Cumbria, Eden Valley, Carlisle and District, Eastern Hull, West Hull, Selby and York, Doncaster Central, Doncaster East, Doncaster West, and Rotherham. This second wave of recruitment yielded a further 24 practices agreeing to participate and being randomised.

The total number of participating practices from these two waves of recruitment was still, at 38, short of our target of 57 practices. Therefore, in a third and final round of recruitment, we approached Birmingham East and North, Heart of Birmingham, South Birmingham, Central Manchester, North Manchester, and South Manchester. In addition to these Trusts we also worked in collaboration with the Scottish Practices and Professionals Involved in Research (SPPIRe) network [SPPIRe evolved into the Scottish Primary Care Research Network (SPCRN) during the time it was involved in the promotion of the LIFELAX trial]. In England, our method was to contact all practices within a particular PCT. In Scotland, SPPIRe operated a different system whereby the node coordinator (there was one coordinator for each of the four nodes – north, south, east and west) approached practices that they knew to be research active, or had expressed an interest in joining primary care trials. A further 14 practices (13 in England, 1 in Scotland) agreed to participate and were randomised following this third wave of recruitment.

With the advent of the National Institute of Health Research Clinical Research Network (NIHR CRN) and its development and support of a portfolio of ongoing trials, we also took the opportunity to promote the trial more widely in England. As a result, some UK PCRN managers contacted the study team asking for further information about the trial. (Many areas had existing PCRNs; in October 2008 the new PCRNs were officially launched.)

Although keen to help the study recruit, the decision of the TSC not to apply to the HTA for a further extension meant that these offers of assistance with recruitment were not taken up. With hindsight, it appears that this decision taken by the TSC was entirely appropriate, considering the number of insoluble barriers identified through the embedded process evaluation (see Chapter 6).

Obtaining PCT R&D approvals

The process of obtaining R&D approval from participating PCTs took varying lengths of time from 1 month up to a whole year. [For one PCT, approval proved impossible to secure, despite numerous unanswered approaches to them. On the advice of the neighbouring PCT's R&D Manager (where we had secured approval) we waited until the two PCTs merged and we were given approval for the newly formed PCT.] In the majority of cases, approval was given within 1–2 months of our application. Most of the delays were caused by disagreements with respect to indemnity issues or honorary contracts. With respect to indemnity, the issue was concerned with where the responsibility for provision of indemnity for the study lay. The principle is that indemnity against negligent harm is available through the NHS indemnity scheme and/or through the GP's own professional indemnity for practice staff. Members of the research team held honorary research contracts with the NHS, and this provided NHS indemnity for negligent harm in respect of their role in delivering the intervention (essentially in training practice staff in the intervention; members of the research team did not play any direct role in delivering the intervention to patients). Professional liability insurance carried by Newcastle University indemnified protocol authors (i.e. the research team) in respect of liabilities arising from negligence in study and protocol design. We made it clear to the Trusts that we did not anticipate there being any claims against either the NHS or the university in respect of negligent harm. The study design had been peer reviewed and the conduct of the study was monitored and reviewed on a regular basis by the funding body (NHS Health Technology Assessment programme) and by the TSC. However, we repeatedly needed to demonstrate to Trusts the professional liability insurance the University had in place to cover for negligent harm caused by the design of the study (as opposed to its execution, which was covered by NHS and GP professional indemnity, as indicated above).

The issue of non-negligent harm was a matter of concern for many PCTs. Our MREC deemed (as is usual for non-commercial studies, especially

those where no novel drug was being used) that there was no requirement for us to have indemnity against non-negligent harm. However, not all Trusts accepted this. These issues were eventually resolved, but the process was burdensome, time consuming and frustrating. We soon learned that the best policy was to send, at the time of application, every document we had ever been asked for by other Trusts in support of our application, even though the standardised R&D approval form was all we were obliged to submit. Our experiences were common to other studies at the time. STOOL also reported a frustrating, burdensome and time-consuming account of the R&D approval process,[19] but it was not just primary care trials of constipation that experienced the vagaries of the Trust approval process.[190]

We were fortunate that all of the PCTs to which we applied were part of consortia. This meant that rather than an individual application for R&D approval being made to each individual PCT, one application could be made to the consortium to which the PCT belonged. LIFELAX did encounter one delay, as one of the PCTs in one of the Consortia would not approve the trial, despite the consortium's lead PCT (which had reviewed the application) recommending that all member PCTs approve it. This issue was resolved after a discussion between the PCT responsible for the review and the non-approving PCT; although the delay was minimal, the frustration was not. Although the standardised NHS R&D form was a move towards a standardised approach by using a standardised application form, each of the consortia had their own application form. The detail required on the forms ranged from the minimal (akin to a study registration form – as LIFELAX was funded by the HTA and peer review was part of the funding process the R&D lead in this consortium required very little information about the methodology, sample size calculation and rationale for the trial, as this had been scrutinised previously) to the comprehensive (akin to the standardised R&D form).

All bar two consortia required that the trial be approved before approaches were made to any practices in their catchment area regarding their participation in the trial. One consortium (part of recruitment area 1) allowed us to approach practices while the governance issues (honorary contracts and individual PCT approval) were being resolved, on the proviso that no research activities were undertaken prior to approval being given. There was a further stipulation from this consortium that before a practice could actually 'go live', the R&D lead needed to decide on whether a practice was 'suitable'. This was an interesting addition to the recruitment process, as this decision about a practice's 'suitability' would have seemed to have been most appropriately made by the REC process; furthermore, the criteria to be applied by the R&D lead in assessing 'suitability' were not transparent. Nonetheless, with LIFELAX having circumvented the SSA process, we understood that there might be a concern from the R&D lead that a practice was not assessed for suitability and we therefore accepted this additional check. However, this check for suitability was also routinely carried out for practices that had already had an SSA by an LREC. The level and methods of checking for suitability are unclear and their effectiveness could perhaps be questioned.

After approving the practices for participation in LIFELAX, one senior partner in a practice deemed 'suitable' had a number of allegations made against him and was suspended, prior to resigning and the practice being taken over by the PCT. The allegations were initially made at the time we were asking for the practice to be approved. This calls into question the effectiveness of the process for assessing practice suitability that was in place locally. In another practice the computer system was replaced by the PCT and this change and subsequent delay meant there were considerable difficulties in searching for participants. This upgrade to practice prescribing systems was being carried out to all practices in the Trust, yet it was not identified by the R&D lead as a potential barrier to timely recruitment.

In another recruitment round (part of recruitment area 2), we were asked by the PCT to recruit practices before any approach for R&D approval from the PCT would be considered. Here the view was that unless there was interest from practices then it was not worth processing the application. This in itself was frustrating as all of the trial materials stipulated that we had PCT approval at the point of writing; we felt that having this approval would demonstrate to practices and patients alike that LIFELAX was a legitimate study and would lend it an air of importance. For reasons of cost and logistics (including the need to have revised patient information sheets reviewed and approved by the MREC, and old versions of the sheets withdrawn and replaced), we did not revise the information sheets. We did have practices wishing to join the trial in the area and so the PCT did eventually need to consider and approve the

study. Fortunately, none of the practices joining the study from the PCT questioned the timing of this approval, and it was in place by the time patients were approached to participate.

Honorary contracts (both applying for them and having them issued) was another source of delay. There was lack of agreement between PCTs on which members of the research team required an honorary contract, what constituted a 'current' Criminal Records Bureau (CRB) check (and what level – standard or advanced – was required) and whether an occupational health check was needed. Some PCTs were prepared to issue a covering letter to act as a 'mirror honorary contract' once they had seen evidence of an honorary contract being issued by another PCT. In a number of other PCTs, a new honorary contract from the PCT concerned was required; in some of these, we were told that a new CRB check would need to be carried out, as those that had been carried out at the start of the trial were no longer 'current'. The University HR department made it clear that it would only process one CRB check per person per study. We eventually managed to get Trusts to accept the initial 'study' CRB check, arguing that it was not a requirement for Trust substantive employees to have 6-monthly or annual renewals of CRB checks, and therefore that it would be inappropriate to apply more stringent criteria to those seeking honorary contracts.

As should be clear from Chapter 2, it was never intended that any members of the research team [with the exception of the researcher (BH) conducting the interviews in the embedded process evaluation study] should have face-to-face contact with patients. Although this changed over time in line with the revised recruitment protocol (described later in this chapter), initially all face-to-face contact for patients was to be with trained members of the GP practice staff. Most members of the research team were only ever to have access only to anonymised patient data, and in a few cases to practice premises and staff, and would not be materially affecting the quality of care received by patients, and so we felt that the stipulations in respect of honorary research contacts appeared overly cautious and added a level of unwarranted bureaucracy, delay and cost.

LIFELAX as a business

An RCT is a huge investment in time, money and people. For a long time it has been acknowledged that in order to succeed, trials need to be marketed and trial managers need to think like marketers.[191]

Trial management involves lateral thinking, good communication, ethical marketing and common sense.[192] From the start of the trial, LIFELAX was looked upon as being very much a small business. We understood that we would need to find GPs and convince them to 'buy into' the study. However, when businesses market a product they are attempting to convince customers that they will gain benefits directly from their purchase of the product. In LIFELAX the marketing task was somewhat different in that we were seeking to gain a commitment from senior GPs to allow their practice to engage in the study, when they themselves would apparently make no direct material gain by doing so. Therefore, from the outset, it was vital for LIFELAX to identify the potential gains and benefits that would accrue from participation in the trial.

Although not specifically stated at the time that LIFELAX was being '*marketed*', the subsequent publication of the Strategies for Trial Enrolment and Participation Study (STEPS) report[193] and the influential 'Marketing and clinical trials: a case study'[194] allow us to retrospectively assess LIFELAX's marketing strategies against these proposed models for success (*Figure 8*).

Developing 'brand values' (Ia)

Brand values define what a brand is and what it is not. Without this, it is impossible to communicate a coherent and persuasive perception of a trial's 'promise' – i.e. what the trial intends to deliver to medicine, doctors, patients, etc. We worked closely with professional designers and graphic artists to develop the LIFELAX brand. We had our own distinct logo, font and colour scheme that featured on all of our trial related materials to render them easily identifiable. The 'promise' of our logo was life and vitality.

Gaining legitimacy/prestige (Ib)

Trials need legitimacy – they need to be positively' tagged' by association with prestigious individuals and institutions. LIFELAX was 'tagged' to the Newcastle University 'brand' (using the recognised crest) and to NoReN/NYReN (PCRN-NE) and its Clinical Director, Professor Greg Rubin. Legitimacy and prestige provide persuasive credibility, which is key to gaining access to decision-makers who decide whether a trial should be supported and maintain engagement. Practice senior partners and staff, particularly those in north-east England, would have been familiar with, and respectful of, both Newcastle University and NoReN/NYReN.

Signalling worthiness (Ic)

It is vital to signal to likely participants that 'this trial will create greater value than the costs (time, effort or money) involved'. In LIFELAX we negated the 'money' cost by securing the SfS funding. This effectively meant that all LIFELAX-related 'costs' incurred by practices would be reimbursed. We were also able to present the training in the behaviour change techniques as a benefit to practice staff (training in such techniques is both costly and difficult to source) that would be generalisable and applicable beyond the LIFELAX study. By highlighting the benefits that changes to diet and lifestyle have on a range of conditions (not just constipation) we hoped to show the value of participation. The aim was to roll out the training in the behaviour change techniques to all participating practices at the end of the trial so this 'value' would be available to all.

Providing simple, complete processes (IIa)

Trials require participants to undertake work – for example, identifying, approaching and recruiting patients, delivering the intervention and completing study documentation – that is additional to their normal duties. Providing them with simple, complete processes reduces the opportunity and financial costs of participation and increases the chances that involvement will be affordable and manageable. We offered assistance with electronic queries to search for patients. We (following the protocol amendment) undertook the consent, recruitment and follow-up processes.

Devising strategies for overcoming resistance (IIb)

Potential participants frequently raise objections. Trials should have standard and persuasive answers to these. Having a persuasive answer for each objection increases the probability of 'making a sale'. This is an interesting premise for LIFELAX. Due to the 'opt in' nature of the practice recruitment process, we intuitively felt that post-enrolment resistance would be low. We were not 'cold calling' practices and trying to convince them to join. However, as shall be seen later in this

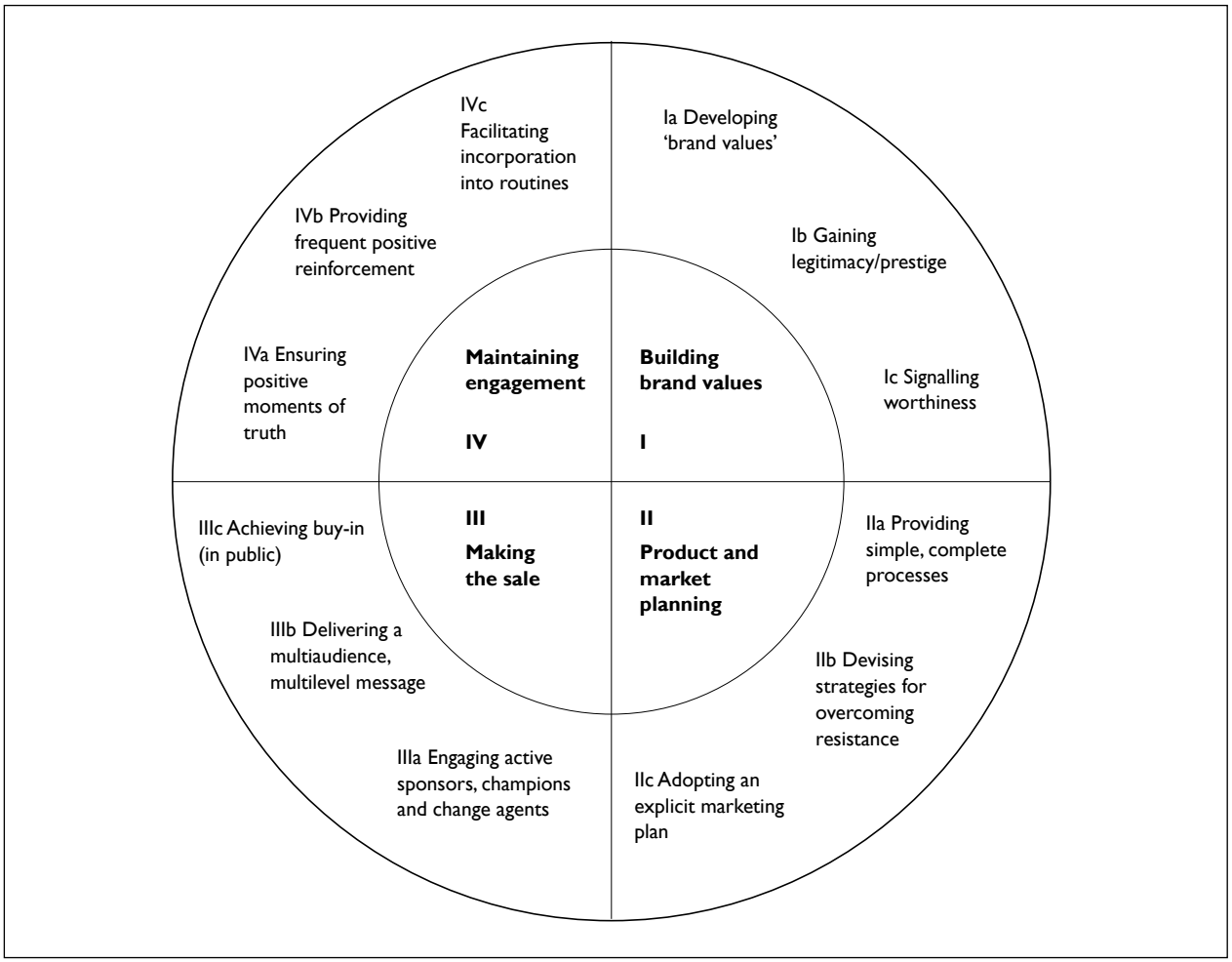


FIGURE 8 *The 12-component reference model.* Adapted from Francis *et al.*[194]

chapter, resistance to participation (barriers) were identified. The strategies we devised to overcome them are also discussed below.

Adopting an explicit marketing plan (IIc)
The marketing of a trial is too important and too complicated to be done informally. A formal marketing plan is required and should include a definition of target market segments (groups that need to buy in to the trial) and the trial's unique selling points (USPs). LIFELAX may not score highly in this component as we did not as such. We were aware that the 'way in' and 'sign up' for practices usually has to be via the senior GPs, rather than the practice nurses, managers. We actually targeted all three in our approach, as we describe below. So in this respect it can be argued that we did adopt a marketing plan, We identified the trial's USP for each of the categories to highlight the benefits of supporting the study.

Engaging active sponsors, champions and change agents (IIIa)
Selling a trial to prospective participants requires persuasion. This requires enrolling sponsors (public advocates), champions (activists) and change agents (facilitators). Trial managers need a network of supporters to spread the message. Persuasion is more likely to occur if the advocate is respected and known personally to the prospective participant. LIFELAX did have local champions (via NoReN/NYReN). However, we failed in our early attempts to recruit public advocates and our patient representatives' activities were confined to TSC duties (though they were extremely supportive of the study).

Delivering a multiaudience, multilevel message (IIIb)
Trials need to convey sales messages through publicity, presentations, training materials, etc. These should be tuned to the distinctive needs of target groups – for example, surgeons are likely to be persuaded by different messages to administrators or nursing staff. Speaking in the language of the person being targeted and addressing their particular pattern of motivation is more likely to succeed than a 'one size fits all' approach. In LIFELAX we understood the importance of this. Our presentations (contents and style) were tailored to fit with our target audience (GPs, nurses or practice managers).

Achieving buy-in (in public) (IIIc)
Public buy-in requires that intended participants announce their commitment to join the trial in a setting where others hear them. This is important because when someone states, in public, that they are willing to undertake an action, then they are more likely to abide by their commitment than if they take a silent decision – that can be forgotten easily. This was not done in LIFELAX. With benefit of hindsight, we wonder whether techniques such as regular publication of lists of signed up practices might have acted as a signal of commitment. Anecdotal evidence of the lack of awareness in practices signed up to the study suggests that in some cases the senior partner did not even announce commitment to, and elicit support from, the rest of the practice team, leading to a lack of awareness of the study and them feeling that they were 'pressed' men and women.

Ensuring positive 'moments of truth' (IVa)
People evaluate organisations (including trial management teams) on the basis of their experiences at moments of truth. For example, if a doctor has a technical question about entering a patient into a trial, she will gain a strong impression of the trial management team's competence by the way that the query is handled. In LIFELAX we had a clear and efficient way of handling queries so that accurate and timely responses were given. We set up a dedicated 'LIFELAX.queries@…' e-mail address so that practice staff could e-mail queries and questions to us directly. This account was checked routinely and the message passed to the most appropriate member of the trial team for response.

Providing frequent positive reinforcement (IVb)
Positive reinforcement for existing participants should be an important part of a trial's participant retention strategy. It is more expensive to recruit new participants than to retain existing participants. We feel that we largely achieved this in LIFELAX. Those practices that underwent training and became active recruiting sites remained committed to the trial until the end.

Facilitating incorporation into routines (IVc)
Activities that become embedded as routines are more likely to be done than one-offs. Trial procedures should be incorporated into the routines of units undertaking the work. Due to the 'stand alone' nature of the patient search and mail out, it is difficult to see how this aspect of LIFELAX could be incorporated into practice routine. With regard to the intervention, we

were concerned that nurses who saw participants on an infrequent basis might feel less confident in engaging with the techniques. Recognising this, we attempted to show how the principles and techniques of behaviour change taught in LIFELAX could be incorporated into routine practice, and so LIFELAX should not be seen as study-specific training.

With reference to the 12 components above, we are able to demonstrate that the LIFELAX marketing strategy used does fit closely to the proposed STEPS model for success, although we did not apply it explicitly in designing and conducting the study (the STEPS publications[193,194] appeared in 2007).

Practice recruitment

Based upon knowledge from previous studies and from feedback from the practices involved in the development of the intervention, and in a bid to target the relevant information to key stakeholders, we sent three copies of all of the study paperwork to the practice. One copy was sent to the senior partner, one to the practice manager and one to the practice nurse. We felt that the trial would be most relevant to the practice nurse and in their letter they were encouraged to discuss participation in the trial with the senior partner or practice manager.

Recruitment of practices was managed in the following way:

- Three copies of a promotional flyer, containing brief details about the study and alerting staff that more information was on its way were sent to staff at each practice as described above.
- In the weeks following this, three personalised study packs (covering letter, information sheets, expression of interest form and SAE) were sent to staff at each practice as described above.
- After 2 weeks, if the expression of interest form was not returned, duplicate reminder packs were sent to practices.

The expression of interest form allowed practices to indicate whether they would like to join the trial or would definitely not like to join the trial and therefore wanted no further information about it. If they required further information prior to reaching a decision, contact details for the trial team were included.

In addition to the mailshot to practices, the LIFELAX team undertook a number of other 'profile-raising' activities:

- contacting relevant PCRNs and asking for their assistance in identifying research active/interested practices
- writing articles for inclusion in PCT and research network newsletters.
- attending PCT working groups, practice staff meetings and PCT nurse training events/meetings to discuss the trial.
- attending PCRN research days and training events.

Recruitment of general practices to LIFELAX proved much more difficult and slow than originally anticipated. In the first round of recruitment (area 1) a total of 306 general practices (from 11 PCTs) were approached to join the study using the method described above (flyer, invitation letter, reminder letter). A total of 168 general practices (55%) responded to the invitation to join the study: 144 practices (47%) did not wish to join the study and did not wish for further contact about it, but 24 practices (8%) agreed to join and were randomised. Overall, 138 (45%) practices did not respond to either the initial recruitment letter or the reminder letter. Moreover, 10 of the practices that were randomised withdrew from the study before undertaking patient recruitment, leaving 14 (5%) practices as potential recruitment sites. *Table 10* shows a breakdown of recruitment activity in each of the recruitment areas. Due to concerns over the low levels of expressed interest and practice recruitment rates, a decision was taken to telephone practices that had not returned a form to the trial team stating explicitly that they did not wish did to participate. Two members of the trial team rang 134 practices out of the 138 that did not respond and spoke to either the practice manager or the practice nurse. After this process we managed to recruit a further three practices to the trial. One of the practices became a recruiting site. The second had very low patient numbers (the search yielding single figures) and decided not to participate and the third withdrew prior to conducting any patient searches. This telephone follow-up of non-responding practices was a very resource-intensive process for the research team (often requiring multiple calls before being able to speak to the targeted individual), and due to its lack of success, it was not used in other recruitment areas.

TABLE 10 *A breakdown of recruitment activity in each of the recruitment areas*

Recruitment area	Number of practices	Number of responses	Responded to say 'no' to LIFELAX	Recruited	Practices recruiting at least one patient in trial
1	306	138	144	24	7
2	456	352	90	14	6
3	352	317	29	6	6
Total	*1114*	*807*	*263*	*44*	*19*

Barriers to recruitment of practices

Due to the concerns about practice recruitment levels in both STOOL and LIFELAX, we considered it was essential to identify the barriers to recruitment to the trials and, where possible, address these barriers. Feedback about LIFELAX and the perceived barriers to recruitment was collected in a number of different ways:

- feedback from GPs, practice managers and practice nurses invited to take part in the study about what they thought were the difficulties of accommodating LIFELAX (this will be further explored in the embedded process evaluation – Chapter 6)
- informal telephone interviews with GPs, practice managers and practice nurses from 'non-responding' practices as part of the recruitment drive described above
- feedback from research-active GPs (colleagues of the members of the research team)
- feedback from members of the extended research team and members of the TSC
- feedback from PCT R&D managers and facilitators
- feedback from the UK Trial Managers' Network
- literature that was being published at the time.

There was a wide range of issues that appeared to be barriers to participation in LIFELAX. Some of them were common to both LIFELAX and STOOL; others were common across all primary care research at the time. Some of the issues were specifically related to the topic and methods of LIFELAX, some to the Research Governance requirements, some to the practice resources. As shall be seen in the chapter detailing the embedded Process Evaluation Study, none of these issues exists in isolation; no matter how small any individual barrier appears to be, both alone, and in combination with others, it can have a major impact upon the successful implantation of a trial. The key issues identified were (no order of importance is implied):

The workload for practice staff

- The burden to staff in identifying potentially eligible patients (i.e. running the searches).
- The burden to staff in posting out study information to patients identified as being potentially eligible.
- The burdensome nature of the LIFELAX recruitment process. There was a lack of nursing/staff time to carry out the informed consent process and baseline assessment.
- The time taken to train staff to deliver the diet and lifestyle intervention arms.
- The length of time needed to deliver the personalised intervention (45 minutes of clinic time + follow-up telephone calls).
- The fear that taking part in a trial might make participants 'constipation' aware and thereby increase the number of appointments about a condition that had been managed successfully to that point with repeat laxative prescriptions.

Practice space

- A lack of consulting space for the initial baseline assessment.
- The space needed to train staff to deliver the diet and lifestyle intervention arms.
- The clinic space needed to deliver the personalised intervention (rooms would be occupied for much longer).

Research and the research process

- Lack of interest in research in general.
- Lack of interest in the LIFELAX research question (as we shall see in the embedded process evaluation there is a very complex relationship in the perception of roles and responsibilities with reference to managing constipation; we were told that nurses were far more likely to deal with patients with constipation than were GPs, yet practice nurses felt that while they monitored drug regimes of patients with constipation the problem was essentially one that other staff dealt with – either GPs initially in prescribing laxatives or community nurses).

- Changes in research governance regulations meant that many of the tasks that researchers routinely carried out to assist practices (e.g. approaching and recruiting patients directly) were no longer possible.
- Paperwork and documentation required for research governance purposes (in particular the formal letter of agreement/contact) discouraged practitioners from taking part in research.

Changes in general practice

- The introduction of the new General Medical Services (GMS) contracts.
- Constipation did not form part of the Quality Outcomes Framework (QOF) and was therefore not as 'valuable' to practices as coronary heart disease, diabetes, etc.
- Research activity was not recognised or rewarded under the QOF.
- Lack of incentives (financial and staff provision) compared to commercially sponsored studies.

Reasons for practice withdrawal

As can be seen from *Table 10*, 16 of the recruited and randomised practices did not go on to become active recruiting sites. Feedback from these practices suggests a range of reasons for this. Being too busy ($n = 9$) was the most common cause cited. There was a concern among the research team that the perceived added workload for practices randomised to the personalised arm might make them more likely to withdraw post randomisation. In fact, we had three practices in each of the arms of the trial give this reason, suggesting that there was no one arm that appeared to be more burdensome than others to practices. Two practices gave staff shortages as the reason for withdrawal. In two further practices, too few patients were identified in the search for potentially eligible patients to make participation worthwhile. In another practice there was no one available to do the searches. In yet another, the senior partner had agreed to join the study without consulting the practice manager. The practice manager was not interested in the project and so the practice withdrew. The final practice that was recruited and then withdrew was the one discussed earlier regarding the complaint to the General Medical Council (GMC) in relation to a senior partner and was actually withdrawn at the behest of the PCT rather than the practice itself.

Protocol revisions and practice incentives to improve recruitment

After the decision was taken to close down STOOL, the LIFELAX research team approached the HTA in July 2005 with a request for an extension to the trial. The HTA was aware that the delays in the trial time line to that point were due in the main to bureaucratic issues outside the control of the research team. By taking an evidence-based approach, we were able to demonstrate to the HTA how we had identified barriers to participation in the study and to propose the measures we would put in place to overcome them. While we were only too aware of the difficulties for practices, we took the opportunity to investigate the recent literature on trial participation from the participant's perspective and to incorporate this in our proposal to the HTA.

Evidence from trials to support the protocol amendment

There was good evidence to suggest that the amendments we proposed to make to the study protocol would allow LIFELAX to achieve the desired recruitment rate for the study. There was evidence from STOOL that the initial recruitment model was not effective. Consequently, this was the first aspect we addressed.

The practice and patient recruitment process in primary care research is much more difficult, more costly and takes far longer than expected.[195] Trial recruitment problems are common, with up to two-thirds falling short of their target, and one-third failing to enrol even 75% of their projected sample. Trials frequently over-run and 10% are abandoned with recruitment failure.[196]

Burden of participating

Taking part in research places 'additional demands' on participants.[196] These additional demands included extra procedures, appointments, time, inconvenience and expense. The revision to the protocol we proposed minimised the number of additional demands taking part in LIFELAX made on participating practices and their staff. We no longer required patients to visit their GP practice to give informed consent and take part in the baseline assessment. Instead, we offered that a member of the research team would visit them at a time and place convenient to them, following 'opt in'

by the patient. This change to the protocol meant that the burden and expense of the recruitment and consent procedure was borne by the research team and not the practice. This amendment had the additional bonus that patients could be visited on an evening or weekend should they wish, and therefore had the potential to increase patient participation rates.

From a practice perspective, this amendment immediately freed up clinic time and space for other activities and reduced the burden for them. For patients with transport or mobility problems, there was an additional benefit as there was no need for them to travel to the surgery for the baseline assessment.

Treatment preferences

Treatment preference and worries about treatment efficacy were also highlighted as potential barriers to participation. In LIFELAX, regardless of the intervention arm (we hoped that those in the diet and lifestyle arms would be able to reduce their laxative use), participants were able to request a laxative from their GP or self medicate using OTC products (the qualitative element of the STOOL study indicated that patients were reluctant to change or give up their laxatives, once an acceptable treatment regimen had been found). We felt that this would lessen these concerns.

Concerns about research

Distrust of, and unfamiliarity with, the research process and concerns about information and consent were also raised as points of concern by participants. We believed that by allowing patient participants to contact the study team anonymously or in confidence to discuss any aspect of the trial, we would be able to lessen this to an extent. At the face-to-face meeting with a member of the team we would be able to explain fully the research process, and clarify why we were doing what we were doing and to what ends. We were also able to explain fully just what data were being collected and why they were being collected. We were also able to explain fully how security and anonymity were achieved and maintained. The benefit of reallocating this task to the research team, as opposed to leaving practices to undertake it, was that there was no time constraint. A researcher was able take as much time as a patient participant needed and was better placed to answer questions regarding the study design and protocol.

The personal touch

It has been claimed that the most important aspect for researchers to control is the patient recruitment process and that during this phase of the study researchers needed to maximise their personal involvement.[196] Gabbay and Thomas[196] believed that most of their recruitment was successful because they undertook it themselves. Working with other health professionals was, for them, helpful at times; however, they found that relying on others to conduct the recruitment was fraught with difficulties. Recruitment problems, they maintained, could be reduced if the research team carry it out. Foy *et al.*[197] recommend a range of ways in which patient recruitment to trials can be improved. Based on evidence from a systematic review of the literature and from seven RCTs, they concluded that the research team should conduct both the consent and recruitment aspects of trials, although current guidance on not releasing patient identifiable data to those outwith the clinical team without the patient's consent, and on the need for 'opt-in' rather than 'opt-out' approaches presents a challenge in this respect.

Copies of the original protocol and the final protocol can be found in Appendix 1. The major changes between the protocols were in patient recruitment (including giving informed consent and the baseline assessment).

Original recruitment protocol (version 2, 18 February 2004)

1. Potentially eligible (by reference to inclusion criteria) patients were identified by practice staff from practice-held records.
2. GPs then screened these patients for contraindications and comorbid conditions that were exclusion criteria.
3. Patients meeting the study eligibility criteria were then written to by their practice and were sent the study information sheets. An appointment at the practice was also made for a future date and details of this appointment were included with the above paperwork.
4. Patients were asked to contact the practice to (1) confirm that they would attend the designated appointment or (2) rearrange a suitable appointment time. Non-attendance at the clinic was taken to imply that the patient did not wish to participate in the study. No reminders were sent to those who did not respond to the initial invitation.
5. Patients wishing to take part in the LIFELAX study were required to attend their GP practice, first, to give informed consent, and, second, to take part in a baseline assessment (on the same day, and subject to informed consent having been given). Practice staff were responsible both for taking the

informed consent and conducting the baseline assessment.
6. After consent and the baseline assessment, participants in the control arm were able to collect their laxative prescription. Participants in the diet and lifestyle arms were required to make a further appointment for the intervention to be given.

Recruitment protocol, version 3+

1. Potentially eligible patients were identified by practice staff from practice-held records with assistance from the NoReN research nurse [the NoReN research nurse post was created to help practices take part in research; as the research nurse held a substantive NHS contract she was able (with permission from the practice) to help with patient identification]
2. GPs then screened these patients for contraindications and comorbid conditions.
3. Patients meeting the study eligibility criteria were then written to by their practice and were sent the study information sheets.
4. Patients also received a form on which they are asked to provide their contact details if they wish to join the study. Patients were asked to return this form to the study team in a prepaid envelope, i.e. an 'opt-in' approach. No reminders were sent to non-responders.
5. When a completed form was received by the study team, they arranged for an appropriately trained person (with an NHS honorary contract and CRB check) to arrange a suitable time and place to take informed consent and conduct the baseline assessment with a patient (as LIFELAX eventually recruited in Scotland and it was not possible to send staff there to take consent and carry out the baseline assessment, this was done over the telephone from protocol V4 onwards)
6. Once informed consent was given and the baseline assessment completed, a copy of the signed consent form was sent to the practice with instruction for them to contact the patient to arrange an appointment for the intervention to begin.

Support for Science funding

One of the barriers to practice participation was the 'cost' to practices in terms of staff time and practice resources. Feedback from research active GP colleagues and from the UK Trial Managers Network suggested that if we were able to demonstrate to practices that there would be no financial penalty to taking part in research that they would be more likely to get involved. To address this, an application was made to the Department of Health (DH) to secure funds to reimburse practices for their time spent on LIFELAX activities via the SfS (ad hoc) funding stream. We worked closely with NoReN (as a holder of Budget 1 funding, NoReN was eligible to receive and disburse SfS funding, unlike the majority of PCTs and general practices) during the application process. We agreed with the DH that all activities would be reimbursed at a Nurse, H-grade spine point 13a equivalent, including NI contributions, superannuation and increments. This equated to approximately £20.00/hour. We felt that this was a generous rate and most of the practice staff involved in LIFELAX would not be employed at as high a grade as this. The costing algorithm we agreed with the DH also took into account the hire of practice space, heating/lighting costs, postage costs and the cost of telephone calls during the trial.

We were able to access funding for both service support costs (in respect of practice activity in identifying, recruiting and consenting patients, and completing study assessments and documentation) and excess treatment costs (in respect of the additional time required to deliver the diet and lifestyle interventions). With the change in the recruitment protocol, informed consent and the baseline assessment were undertaken by the research team and the NoReN research nurse and so no reimbursement (in the form of service support costs) was due to practices for time spent on these activities. Practices were, however, asked to identify patients from records and send them a study pack. The rate of reimbursement for this was £7.31/patient. However, due to the way the SfS funding was allocated, this payment was dependent on a patient joining the study. This meant that if practices did write to all eligible patients and none decided to take part in LIFELAX, a claim could not be made. As a goodwill gesture, practices were paid a 'site set-up' fee of £50 from the project budget to cover the patient search and mail out, just in case no participants were recruited from a particular practice.

Excess treatment costs could also be reimbursed to practices. However, the DH was exacting on what constituted excess treatment. Only payments for genuine 'excess treatment' costs could be made. The DH was of the opinion that for the duration of LIFELAX each participant would be entitled to one appointment at their practice for their constipation and, as such, this appointment was

not 'excess treatment'. It was only trial activities in excess of this appointment that would qualify for reimbursement. As the control arm did not generate 'excess treatments' (it was standard care) no claim could be made. For practices randomised into either of the diet and lifestyle intervention arms, claims could be made as there was some excess treatment time for each patient (5 minutes per patient in the 'standardised arm' and 85 minutes per patient in the 'personalised arm'); per-patient claims were agreed with DH at £2.73 and £46.35, respectively. While we recognised that these rates were vastly short of industry trial rates, and LIFELAX could not be considered to be a 'cash cow', we were confident that practices would not face any financial penalty by joining our trial.

Importance of research and constipation

One of the major frustrations we encountered when recruiting practices was the perceived lack of importance GPs attached to the research question posed by LIFELAX. We understood that it was most probably practice nurses who would deal with patients with constipation and attempted to target them with our trial literature (see Chapter 6 for a fuller discussion on practice nurses' interests); however, in most cases it was a GP who would make the final decision about participation and unless they were convinced of the importance of the study there was little chance of the practice participating. Due to the new GMS contract and the QOF, there was less motivation for GPs to sacrifice staff and clinic time for an activity that was not part of the QOF (regardless of the SfS reimbursement). Hitting QOF targets was the priority in most practices.

It was ironic and frustrating that the majority of QOF target conditions (obesity, coronary heart disease, etc.) would benefit from changes in diet and lifestyle and so the training offered by LIFELAX on behaviour change in these areas would have been appropriate to the QOF topics as well as constipation (which was not part of the QOF). It was interesting that a number of the nurses who we worked with on the trial saw the skills they learned were generalisable and could form part of their routine clinical practice.

Patient recruitment

Identifying patients in practice

While it could be argued that LIFELAX had some success with the number of practices initially recruited into the trial (75% of the target) the number of patients from within the recruited practices to join the trial was far short of target. Patient recruitment was difficult right from the point of identification from practice records. What we had envisaged as being a routine first step in the process proved to be a hurdle for a number of practices.

We had commissioned a bespoke 'electronic query' that practices could use to help identify eligible patients from their databases. The query was designed to be used on the EMIS practice computer system, widely used in north-east general practices. Not all practices used EMIS. Even in EMIS practices, implementing the query was not always straightforward. The query was designed to be 'read by' the practice database, but it soon transpired that not all practices had staff with the IT skills needed to 'run' a query of this nature. The electronic query that we had hoped would reduce practice workloads actually proved to be more burdensome.

As all of the systems had search and query facilities with which practice managers and support staff were familiar, most practices preferred to conduct their own searches using their own search techniques. It soon became apparent that there was a great deal of variation between practices on the level of detail recorded on their databases and a lack of consistency in coding diagnoses. Using a diagnosis of 'functional constipation' often meant that no eligible patients were identified. Very few practices recorded this information. With this in mind, we asked for the searches to be 'built up' using either a diagnosis of functional constipation or three or more laxative prescriptions in the previous 12 months. With the introduction of the QOF we were aware that some practices in one area in particular (area 3) were prioritising (in terms of ensuring accurate and up-to-date coding) the patients and conditions that would form part of the QOF data submission process.

The account thus far may appear to present a very negative picture about the abilities of practices to carry out research. There was indeed a great deal of variability in the time and effort it took for us to recruit, train staff and for them to write out to patients (from 10 days up to 1 year). However, it must be stressed that, despite huge workloads and administrative and bureaucratic demands, those practices that did engage with LIFELAX did so fully and worked tirelessly to support the study.

Recruitment of participants

The first participants were recruited to the LIFELAX trial in July 2005. Poor response to the practice recruitment mail out to patients (as

indicated above, only one letter of invitation, with no reminders, was allowed by MREC), and lack of attendance at scheduled baseline assessment clinics were experienced in all active sites recruited in the early days of the trial (using the burdensome V1 protocol). As soon as this became apparent, plans to amend the recruitment protocol began.

Barriers to recruitment of patients

As discussed above, it appears that the number of patients we expected to find and recruit in practices was lower than we had anticipated.

Conversations with nurses, and practice managers highlighted a number of reasons why they thought that people were not participating in the trial. It is interesting that some of the reasons mirror what patients said when they rang the LIFELAX trial team to discuss participation.

Because most of the practices in the trial were from deprived wards, with low socioeconomic status, practices thought that their patients probably would not be interested in research and would probably not read (or be able to comprehend) the information sheets sent to them (despite our efforts to write in a user-friendly and accessible manner). They also expressed concern at the questionnaires and daily diary as being particularly onerous and complex to complete. Based on experience, practice nurses also thought that their patients, in most cases, would not engage with any aspect of behaviour change.

Patients who rang the trial team often reported research as 'not being for them'. They told us that they were not eligible as they did not have constipation and therefore could not take part. Their evidence for not having constipation was that they were able to 'go' every day (even though this required them to take laxatives which, by our definition, meant they had constipation). This perception of 'not being constipated' and therefore being ineligible reflects experience in the STOOL trial[19] and is therefore a major threat to the ability to recruit prevalent cases. However, as discussed in Chapter 2, the option of opportunistic recruitment of incident cases (new presentations of constipation) was deemed inappropriate from the outset of the trial.

One potential participant went to great length to point out that they 'knew all there was to know about healthy eating' and that nothing their nurse could say would be new and therefore participation was 'rather pointless'.

Due to comorbidity, a higher proportion of patients than that originally estimated by the research team were taking high-dosage codeine-based pain-killers and failed to meet the trial inclusion criteria.

Recruiting the required number of participants

From the 19 practices that recruited participants for LIFELAX, 1473 patients were identified as being eligible (an average of 77 per practice, higher than our anticipated number of 40 per average practice). The final number of patients recruited to the trial was 154, just under 10% of those eligible. In our initial power calculation for the trial we had expected that 75% of eligible patients would consent to be randomised to take part in the trial. Ultimately, the consent rate proved to be nearer to 10%. Using this figure, the size of the recruitment task becomes apparent. In order to recruit 1500 participants, LIFELAX would need to have identified 15,000 eligible patients. Based upon our experience, we would need to have recruited in the region of 200 practices.

Summary and implications

The implementation of the LIFELAX trial appears to have been unsuccessful for several reasons, related both to procedural issues (resulting from changes in ethical review and research governance processes) and to disappointingly low levels of interest and participation at both a practice and a patient level.

It was acknowledged by both the funding body for the trial (HTA) and the TSC that LIFELAX was operating at a time of considerable change and uncertainty around ethical and research governance issues. The process of seeking a favourable opinion from an ethics committee underwent several major changes during the duration of the trial. The initial approach LIFELAX made to MREC used the paper-based MS WORD form. The application system then underwent several electronic iterations, first using the 'FORM FILLER' program, and then the online COREC form, the National Research Ethics Service (NRES) form and the Integrated Research Application System.

Ethics committees reacted to a number of landmark documents and events, including the report of the Alder Hey inquiry,[198] the European Human Rights Act[199] (and its implementation) and preparation for the enactment of the EU Clinical Trials Directive. At this time the guidelines to

which ethics committees adhered became more prescriptive, and committees became more risk aware and took measures to mitigate risk where possible. The guidance from COREC, at times, appeared to be inconsistent and inflexible, and anecdotal evidence from meetings with other trial managers at the UK Trial Managers Network annual meeting suggests that the differences between RECs were immense. Although LIFELAX had a good working relationship with its MREC, the process of ethical review was, and continued to be across the study's lifetime, increasingly bureaucratic.

The publication of the Research Governance Framework[200] created further challenges, with guidance and decisions taken at a local level appearing to be, at times, and at least, contradictory to national advice. The need for all members of the core research team deemed to be 'hands on' (including those such as the statistician and health economist, who were never expected to interact with practices, their staff or patients, or to have access to patient identifiable data) to undergo a full occupational health check (including, in some instances, throat swabbing) seemed to be time consuming, resource intensive, mildly unpleasant and a somewhat unnecessary procedure. Similarly the securing of honorary contracts was rather challenging. The information at a local level as to which members of the research team required an honorary contract was often contradictory, ranging from any person involved with the running of the trial to only those making visits to Trust premises, handling (identifiable) patient data or meeting patients. Although we welcomed the move by Trusts to implement the Research Governance Framework, the variability in interpretation of it and the lack of resources in some Trusts to implement it created a burdensome, often inefficient and slow process. These experiences are mirrored by others researchers undertaking studies in similar settings at a similar time.[201–203]

In addition to the inevitable delays created by these developments, one of the major issues of concern to both the research team and the TSC was the necessity for participants to 'opt in' to LIFELAX and the apparent removal of contact with the research team until much later in the research process. This model has major implications for health services research in the future.[204] By implementing such a model, one immediately decreases the likelihood of participation and increases the risk of participation bias.[205] Communication between the trial team and the participant is crucial to the success of a trial. Opportunities for those most familiar with the study design and processes (i.e. the research team) to explain the trial or discuss any aspect of participation diminish once the GP practice becomes the primary contact point for information in the early stages of the trial and the 'gate-keeper' to trial participants. While practices in LIFELAX were happy to deal with medical queries arising from participation in the trial, they were reluctant and lacking in confidence to discuss general questions about the study, trial design and general participation, as they felt that this was the remit of the research team. Initial communication with potential participants was by covering letter from the GP, accompanied by the PIS. The information required by COREC/NRES to be included in the PIS is very detailed and complex. Our concern was that the PIS might appear so daunting that potential participants would simply ignore it rather than read it, and would either decide not to participate or would not be fully informed, as required for the consent process. Having successfully used a 'brief' and 'full' PIS system in another RCT concerning patients with ulcerative colitis,[206] the same approach was used in LIFELAX. It was hoped that interested patients would be able to see from the brief PIS the essentials of what the study entailed and then, should they wish to participate, they would read the full PIS prior to giving consent.

The LIFELAX trial also coincided with the introduction of the new GP contract, including the QOF. Practices were heavily involved in setting up the necessary audit and IT systems required to meet the quality targets associated with this contract. As the new contract offered minimal incentives for research, any research activities were viewed by many GPs and their practice staff as a luxury and an unwelcome distraction from the other demands of practice life after the adoption of the new GMS contract.

The feedback that we gathered from both participating and non-participating practices suggests that there was a perception that the cost of taking part in LIFELAX was too great in terms of time, space and practice resources. For some, constipation was not a sufficiently interesting or important topic, a barrier also encountered in the STOOL trial.[19] The barriers to patient participation are less clear. Socioeconomic status may have been a factor – so too might the lack of understanding as to the pragmatic nature of the

trial with regard to current and future laxative use. In STOOL, GP participants suggested that their patients would be unwilling to change from their preferred treatment regime, particularly if it were currently being successful.[19] It may be that in LIFELAX there was reluctance from potential participants to give up a strategy that worked for one in favour of another that may not. It may also be the case that constipation is not such an important or interesting topic for patients, as well as GPs and practice nurses, especially for those who are taking laxatives and are not currently constipated, at least by their own definition.

Chapter 5
Results

Following the recommendation of the TSC not to seek a further extension for the LIFELAX trial it was agreed with the funders that patient recruitment should cease, but follow-up should continue for already recruited participants. Due to the low number of patients in the trial, and therefore the lack of statistical power, it was agreed that we would not carry out a formal analysis of effectiveness, as anticipated in the original proposal. More specifically, we agreed that we would not conduct any hypothesis-driven statistical analyses. Rather, we agreed that our analysis of patterns of response to the patient-reported outcome measures would be largely descriptive.

As LIFELAX used a range of data collection tools (some previously validated, but in other populations, and others developed specifically for the trial) it was agreed to be beneficial to collect data on completion rates, item response rates, measures of validity and reliability, and marginal comments (indicative of acceptability and comprehensibility of the tools) to inform future trials that propose to use these tools in similar populations and conditions. This we do below for the self-completion questionnaire at baseline, 3, 6 and 12 months.

As psychometric properties of validity and reliability of existing scales (e.g. PAC-SYM and the PAC-QOL) may vary according to population and setting, we undertook these analyses on the baseline data in the belief that it would contribute to a general understanding of the performance of these measures in our sample and the general body of knowledge regarding the chosen instruments.

Due to the low number of participants it was not possible to conduct the formal comparative analysis of cost-effectiveness originally planned. A lesser level of comparative cost-effectiveness is presented, along with a descriptive analysis of the costs of living with, and managing, constipation.

Baseline characteristics of the LIFELAX participants

Here we report on the baseline data collected via the self-completion questionnaire and the face-to-face interview. Daily diaries were also completed for 6 months from the date of the start of the intervention. Diary data will be reported separately (below) from the two baseline measures. Further reporting on the effects on HRQoL at baseline can be found in the economic evaluation section below.

Baseline postal questionnaire

This questionnaire collected the following data:

- basic demographics (age, education, employment, etc.)
- experiences of constipation (PAC-SYM[127] and PAC-QOL[38])
- health in general
- lifestyle and mobility
- usual eating habits [Dietary Instrument for Nutrition Education (DINE)[139] and a fluid counter]
- satisfaction with treatment
- anxiety and depression [Hospital Anxiety and Depression Scale (HADS)[207]].

Baseline face-to-face questionnaire

This questionnaire collected the following data:

- general bowel health
- use of prescription laxatives (length of time taking prescribed laxatives, use in previous 7 days, class of laxative)
- use of OTC laxatives (length of time taking OTC laxatives, use in previous 7 days, class of laxative)
- the main thing participants wanted to achieve by taking a laxative
- participant-defined 'successfully managed constipation'.

Baseline postal questionnaire

Demographics

The number of participants recruited by a practice ranged from 2 to 24; the average number of participants recruited by a practice was approximately eight. Patients came from 19 practices in 13 different areas. In total, 141 (92%) of the possible 154 self-completion postal questionnaires were returned, although not all data items were completed by all respondents.

Overall, 140 respondents provided details of gender (61 men and 79 women). Dates of birth were completed in 137 of the returned questionnaires. Based on age as calculated from date of birth and date of questionnaire completion, the youngest participant in the study was 51 years old, the oldest was 96 and the average age of participants was 71. On average, male participants were 3.5 years older than female participants. In the personalised arm the average age was 69, in the standardised arm the average age was 72, and in the control arm it was also 72. Of the 139 responses to the question asking about current situation in relation to paid work, 122 participants were retired, three were in full-time work, four in part-time work and two did not work as they were looking after their home and family. Eight participants were unable to work due to long-term sickness or disability.

Of the respondents 11% had remained in education beyond 17 years of age, whereas 44% of participants had no formal qualification. Only one respondent in the sample was not white, listing his/her ethnic group as 'black'.

PAC-SYM

The PAC-SYM is a 12-item scale measuring stool, rectal and abdominal symptoms. Respondents report the severity of each symptom on a scale from 0 to 4, (with '4' representing the greatest severity). An overall score (PAC-SYM global score) is computed by taking the average item response across the 12 symptoms. The three subscale scores are computed in the same manner, based on the symptom groupings (abdominal – four items; rectal – three items; stool – five items); algorithms for data imputation in the case of missing data mean that subscale scores can be calculated when one or two items in the subscale are missing. The mean scores and standard deviations for the PAC-SYM subscales and global score can be found in *Table 11*.

Figure 9 shows a histogram of the distribution of responses on the PAC-SYM global scale. This provides some evidence that there was a ceiling effect (patients scoring the lowest possible score at baseline, and therefore with no 'capacity' to capture improvement over time) in the study population.

In the development of the PAC-SYM,[127] Cronbach's alpha for the total PAC-SYM score was reported as being 0.98. Subscale Cronbach's alphas were 0.80 for stool symptoms, 0.84 for abdominal symptoms and 0.87 for rectal symptoms. Our findings were consistent with these figures with Cronbach's alpha for the global score being 0.91 and the subscale alphas being 0.84 for stool symptoms, 0.87 for abdominal symptoms and 0.81 for rectal symptoms; all of these values exceed the criterion of 0.70, indicative of adequate internal consistency reliability at the group level.[208]

The PAC-SYM mean scores suggest that the level of constipation symptoms experienced by our sample was low. This is supported by evidence from the objective measure of bowel movement frequency collected in the daily diary. The mean number of daily bowel movements was 1.5. This again supports the findings of the STOOL report[19] that patients did not define themselves as having constipation, once a preferred pattern of bowel movements was established, regardless of whether it took the use of regular laxatives to achieve this.

TABLE 11 *Mean scores (and standard deviation) for the PAC-SYM subscales and global scales*

PAC-SYM	*n*	Minimum	Maximum	Mean	SD
Abdominal	123	0.00	3.75	1.07	0.92
Rectal	119	0.00	4.00	0.74	0.92
Stool	122	0.00	3.25	1.38	0.94
Global	120	0.00	3.17	1.10	0.79

SD, standard deviation.

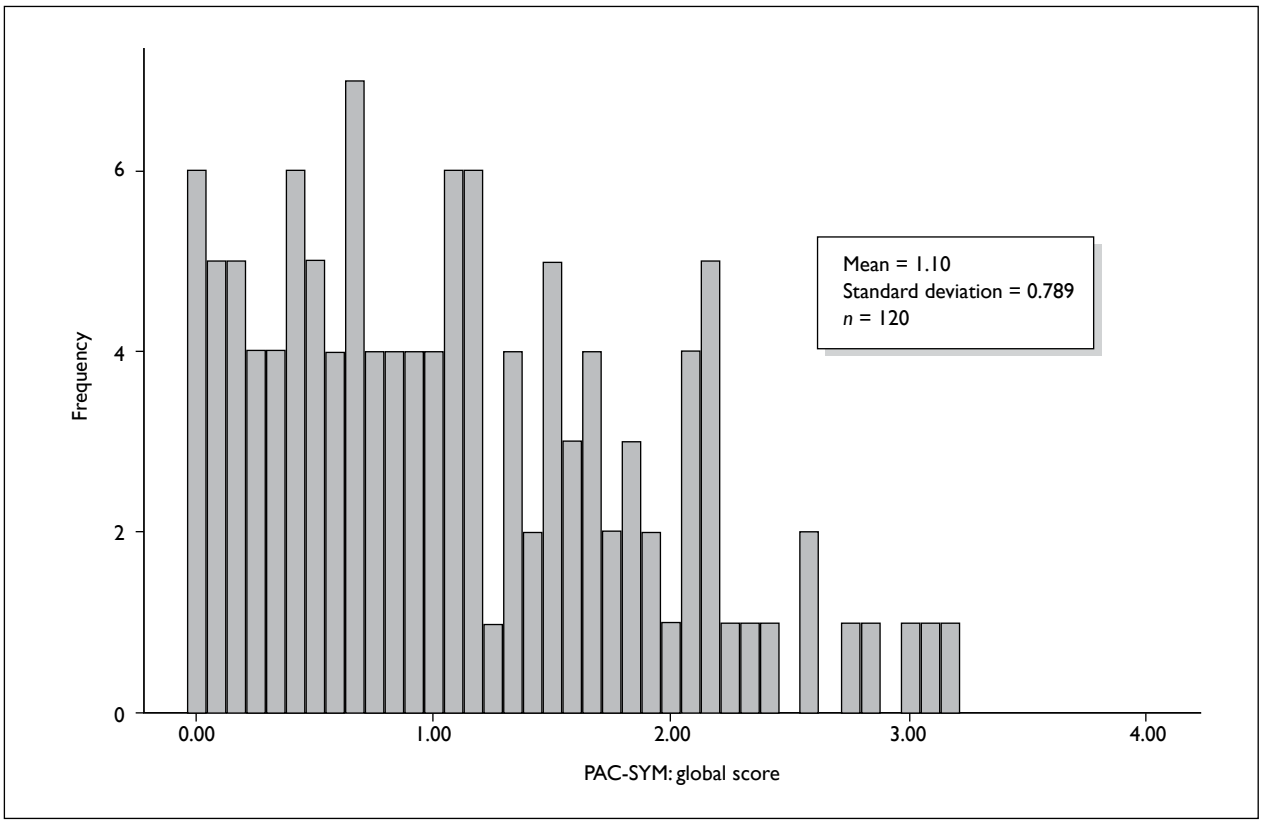


FIGURE 9 *Distribution of patient assessment of constipation – symptoms (PAC-SYM) responses.*

PAC-QOL

The PAC-QOL questionnaire was developed as a patient-reported outcome measure to evaluate the impact of constipation on QoL over time.[38] In development work, the PAC-QOL scales have been established as being internally consistent (Cronbach's alpha > 0.80 on each of them). Our findings were consistent with this. Cronbach's alpha for the 28 items forming the global score was 0.93. For the subscales (dissatisfaction – five items; physical discomfort – four items; psychosocial discomfort – eight items; worries or concerns – 11 items) the Cronbach's alphas were: dissatisfaction 0.86; physical discomfort 0.89; psychosocial discomfort 0.87; worries or concerns 0.93 – again, all in excess of the threshold level of 0.7 indicative of adequate internal consistency at the group level.[208]

The correlations of the PAC-SYM and the PAC-QOL global scores at baseline were in line with what we would expect, with there being a greater impact upon QoL with increased symptoms ($r = 0.76$, $p < 0.01$).

The box plot shown in *Figure 10* offers some suggestion that the groups were not evenly balanced with respect to constipation-related QoL at baseline.

Longstanding disability and mobility

Overall, 73% of respondents reported having a longstanding disability or infirmity. The distribution across the intervention arms was not even, with 84% of respondents in the personalised intervention arm and 71% in the standardised intervention arm reporting this. In the control arm it was 67%. In total, 86% of respondents reported that their disability or infirmity limited their activities. As, due to small numbers of patients, we are not able to analyse formally the effectiveness of the intervention strategies, this baseline imbalance is not such an issue. However, any intervention that requires people to make changes to their lifestyle in terms of being more mobile and active would need to consider the level of disability or infirmity in its population.

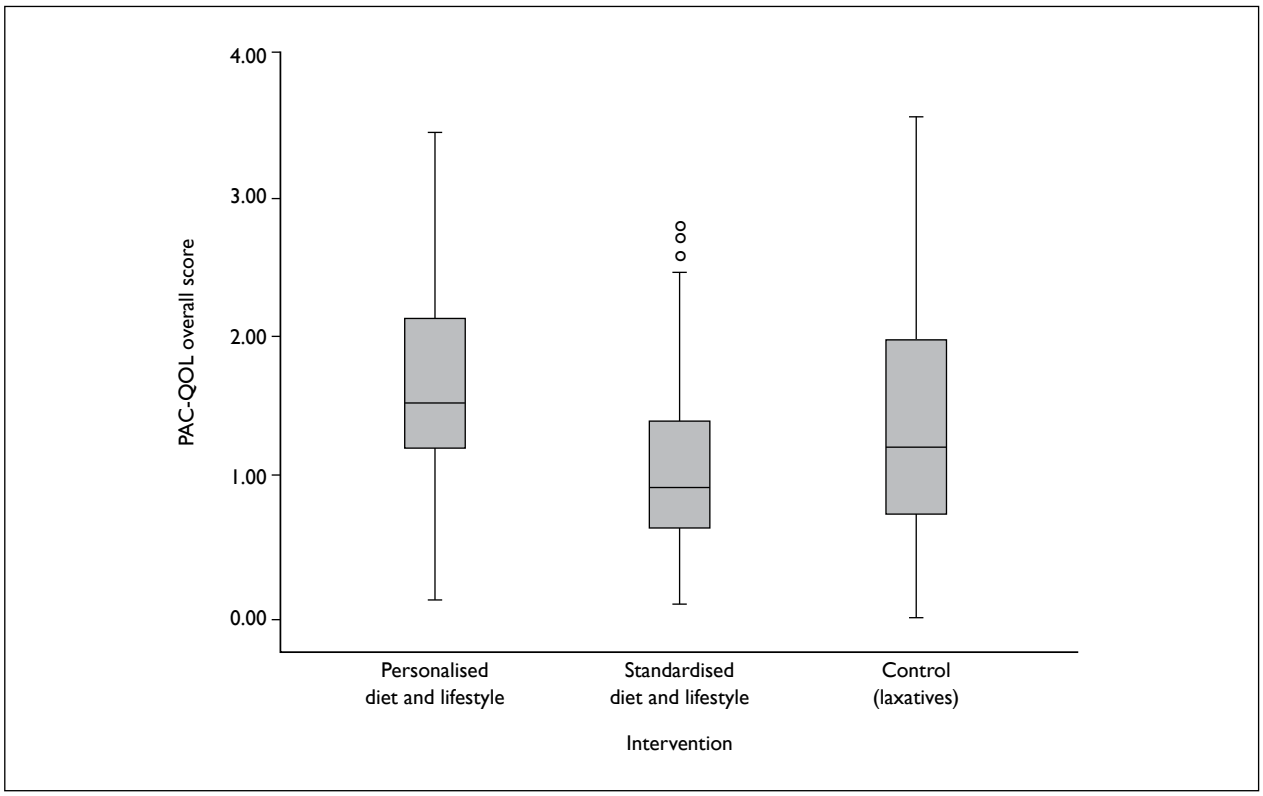


FIGURE 10 *Box plot of the PAC-QOL overall scores.*

None of our sample reported that they were either bedbound or chairbound at baseline. However, the groups were not well balanced in terms of the assistance they needed in order to carry out an activity such as getting up from their chair or bed and crossing the room: 76% of the control group reported they could do this without any assistance, whereas only 42% of the personalised intervention group and 63% of the standardised intervention group did not require assistance.

In terms of being able to undertake any vigorous activities, 59% reported that they would be unable to undertake these and 36% that they could but with difficulty. Again there was an imbalance in the groups with 74% of the personalised group reporting that they were unable to undertake any vigorous activity as opposed to 46% in the control group and 59% in the standardised group.

This finding that the control group was somewhat 'fitter' than the other intervention arms was consistent in all of the other questions that covered functions, such as bathing and dressing self, walking 100 yards and walking half a mile. As stated earlier, although not relevant to the analyses reported here, it may have had an impact on the intervention as not all arms were the same.

Diet

The data on the food and drink that we collected at baseline were intended to be used to explore changes in consumption over time, as each participant took part in the trial. As we are not able to provide such analyses, here we describe the baseline dietary data.

We collected data on the amount of bread (number of slices/rolls) consumed each day. Due to the range of bread types and their fibre content levels, and the contents of the other elements of each participant's diet, it is difficult to fully assess the impact of bread consumption on bowel health and function. Nonetheless, it is possible to express some generalities. White bread is lower in fibre than a granary or wholemeal alternative. In our sample 47% did not consume any white bread at baseline; 44% ate at least one slice of wholemeal bread per day, but 55% reported that they did not eat any wholemeal bread. It is difficult to say whether these figures have a significant role to play in the bowel function of our sample, but it does suggest that there were a significant number of people who could have made a switch from white to granary or wholemeal bread and, depending on the remainder of their diet, this might have had an impact on their bowels.

With regard to breakfast cereal, we collected data on the frequency that different types of cereal were consumed. Sugary cereals tend to be lower in fibre than porridge/wheat/muesli or bran-type cereal. In our sample only 8% reported eating sugary breakfast cereals daily with >70% never eating this type. Forty-two per cent of the respondents ate porridge/wheat/muesli cereal daily and a further 16% ate a bran type cereal daily. This would suggest that, in terms of the breakfast cereal of choice in our sample, those cereals that can benefit bowel health were being most frequently consumed. The scope for dietary improvement in this respect may therefore have been quite limited.

Approximately 41% of respondents said that they ate more than one serving of rice or pasta per week. Again we know little about the impact of this on bowel function; however, it does suggest that rice and pasta were not 'alien' foods to this population and that as wholemeal/brown varieties are available they could be incorporated into the diet without radical changes to current eating patterns.

Potatoes were eaten more frequently than rice and pasta, with 28% of the sample reporting that they had at least one serving of potatoes each day. We do not know from our data whether the skins of the potatoes were eaten too, so can draw no firm conclusion as to the fibre contribution potatoes made to the diet.

Vegetables were eaten by most people on most days with only 5% reporting eating less than one serving of vegetables per week. Pea and bean/lentil consumption were recorded as separate categories to 'vegetables'. Approximately 70% of respondents reported eating at least one serving of peas per week and 54% reported eating at least one serving of beans/lentils a week.

Only six respondents (4%) said that they ate less than one serving of fruit in an average week. We were aware that eating fruit and vegetables is often difficult for older adults with dental issues; however, it would appear that the majority of respondents could eat these types of food and potentially increase consumption to the recommended five portions of fruit and vegetables per day.

Using the fibre calculator from the DINE questionnaire,[139] upon which the fibre items in the baseline questionnaire were based gives us insight into the amount of fibre our sample was consuming at baseline. (Although the DINE was designed to be used in a consultation setting we found it to be an effective method for capturing data on the amount of fibre consumed, as it referred to 'servings' of particular food rather than requiring respondents to carry out any measuring or weighing prior to reporting.) The average score was 34, which falls into the 'moderate' consumption category. This does suggest that while fibre consumption was not low in our population, there was potential to increase consumption to the 'high' category recommended by the DINE authors.

With regard to fluid consumption, 85% of our sample reported that they drank less than the recommended eight glasses of water a day. This finding in itself is not unsurprising as we do know that the urge to drink decreases with age and often there is a worry that drinking more leads to more frequent visits to the toilet which can be inconvenient to people with mobility problems. However, hot drinks such as tea and coffee were consumed very frequently and although water may not be consumed to the level recommended, it appears that with the levels of consumption of fruit and vegetable juice, hot drinks and soft drinks (sugared and sugar free) the amount of fluid consumed is in keeping with the guidelines.

While we acknowledge that the baseline data may not tell us exact quantities of which foods make up the daily diet of our sample, they do provide a guide to the intake of our sample. It would seem that there were a number of areas in which changes to diet could be made and this may have an impact upon bowel health.

Satisfaction with prescription of laxatives

Evidence from the STOOL trial[19] suggests that once someone has found a laxative regime that works satisfactorily then they would prefer to remain on it and not embark upon a new regime. When designing the LIFELAX intervention we were able to take this into account and rather than requiring people to give up on their laxatives (prescription or OTC) we made a decision to allow people to continue taking laxatives. We had hoped that, for those embarking on any diet and lifestyle changes, over time their reliance on laxatives would lessen as the changes began to improve bowel function.

From our sample, 60% of respondents indicated that they were satisfied with the ability of

their prescription laxatives to treat or prevent constipation; 53% were satisfied with the way in which the prescribed laxatives relieved the symptoms of constipation; and 55% of respondents were satisfied with the amount of time it took for the prescription laxatives to start to work.

A total of 68% from our sample reported that they did not experience any side effects from taking their prescribed laxatives. Only 3% reported that they had any difficulty taking the laxative, as prescribed by their GP, in its prescribed form, and only 9% reported that they had any level of difficulty planning when to use their prescribed laxatives; 80% of the respondents said that it was convenient to take their laxatives as prescribed and only 9% felt that taking their laxatives was not a good thing; 70% of our sample reported that, taking everything into account, they were satisfied (satisfied, very satisfied or extremely satisfied) with their prescription laxatives. All of these data suggest that there was little reason or incentive for our population to give up their prescribed laxatives, a finding that is entirely in keeping with the findings in the STOOL report.[19]

PAC-SYM, PAC-QOL and anxiety/depression

Studies investigating the link between psychological illness and disturbed defecation suggest that people with anxiety and depression often have bowel symptoms, with depression being positively associated with constipation[209] and anxiety with increased bowel frequency.[210]

On the HADS, each item is marked on a four-point (0–3) response category. Scores can range from 0 to 21 for anxiety and 0 to 21 for depression. These scales are independent. A score of 0–7 for either subscale could be regarded as being in the normal range, with a score of ≥ 11 indicating the probable presence of disorder and a score of 8–10 being just suggestive of the presence of anxiety and/or depression.

In our sample the mean scores on the HADS show there was no evidence of anxiety or depression either in the group as a whole or arm by arm (*Table 12*).

Although there was no evidence of even 'probable' anxiety or depression in our sample, there was evidence that these scales did correlate with the global scales of the PAC-SYM and PAC-QOL (*Table 13*), providing further evidence of the construct validity of those measures. As stated earlier, the mean PAC-SYM and PAC-QOL scores suggest that although our sample did not experience extreme symptoms, as symptom scores rose so too did the impact upon QoL. These findings are entirely consistent with the view that people who experience greater symptoms of constipation experience both higher levels of depression and impact upon their QoL. Previous research[210] indicates that anxiety is linked to

TABLE 12 *Mean (standard deviation) HADS anxiety and depression scores*

		HADS	
Intervention arm		**Anxiety**	**Depression**
Personalised	Mean	1.10	0.97
	n	31	31
	SD	0.65	0.53
Standardised	Mean	0.77	0.69
	n	65	63
	SD	0.63	0.43
Control	Mean	0.88	0.71
	n	44	44
	SD	0.65	0.36
Total	Mean	0.88	0.76
	n	140	140
	SD	0.65	0.44

SD, standard deviation.

increased gut transit time. Our results are at odds with this finding as our anxiety scores were also positively correlated with constipation symptoms. As our population's mean anxiety score was not clinically significant, it would be both naive and erroneous to expect evidence of increased gut transit time in this case. It is understandable that people experiencing constipation may feel more anxious and perhaps this is one way to account for our findings.

Baseline face-to-face questionnaire

General bowel health

We began our face-to-face interviews with a very broad open question 'Thinking back over the last month or so, how have your bowels been in general?'. On the advice of the clinicians attached to the study, a question such as this served a very important role. While it focused the interview on bowel health rather than general health, it also allowed interviewees to talk about themselves. There was a concern that often people did not have an avenue to talk about their bowels and a question such as this would be a welcome opportunity to talk about any aspect of their bowel health before moving to the more specific structured items. This was not designed to be an analysed question.

Over 45% of our sample had at least one bowel movement per day during the 7 days prior to interview. As normal frequency of bowel movement ranges from at least three in the previous 7 days, it is worthy of note that only 7% reported fewer than this number of motions per week. Over one-third of our sample passed a stool without straining in the 7 days prior to their assessment. However, two-thirds did strain and nearly 20% reported straining either on most days or daily.

In total, 36% of participants reported the absence of hard or lumpy stools, but about one-third of the sample experienced at least one or two per week; 88% of respondents experienced a feeling of incomplete emptying of their bowels, and half of them said that they felt that at least on one occasion in the previous 7 days when they were answering the call to stool, the stool could not be passed; and 30% of people had needed to press around their bottom to assist with the passing of a stool on at least one occasion in the week before interview.

Use of prescription laxatives

In our sample, over 30% of respondents had been taking a prescription laxative for 10 years or longer, and 90% had been taking a prescription laxative for more than a year. A breakdown of the duration for which respondents had been taking laxatives can be seen in *Figure 11*.

Nearly 90% of our participants had used a prescription laxative in the previous 7 days, with in excess of 41% of them being prescribed a stimulant laxative by their GP; 30% had been prescribed a second laxative and 5% of our sample was prescribed a third.

Half of the respondents had never taken an OTC laxative and approximately 15% had been taking them for 10 years or more.

Main thing participants wanted to achieve by taking laxatives

This was an open-ended question. The responses were varied, including references to an end to the feeling of lethargy associated with constipation and a belief that if the bowels were not completely emptied they could make you ill. The most common achievements that participants wished from their laxatives were 'ease' of stool; soft consistency for their stools; frequency and regularity in their visits to the toilet. As only 7% of our sample fell outside the 'normal' frequency

TABLE 13 *Correlation between the PAC-SYM and PAC-QOL (global) and the HADS scales*

		HADS	
		Anxiety	**Depression**
PAC-SYM: global score	Pearson correlation	0.306	0.237
	n	120	120
PAC-QOL: global score	Pearson correlation	0.553	0.381
	n	135	135

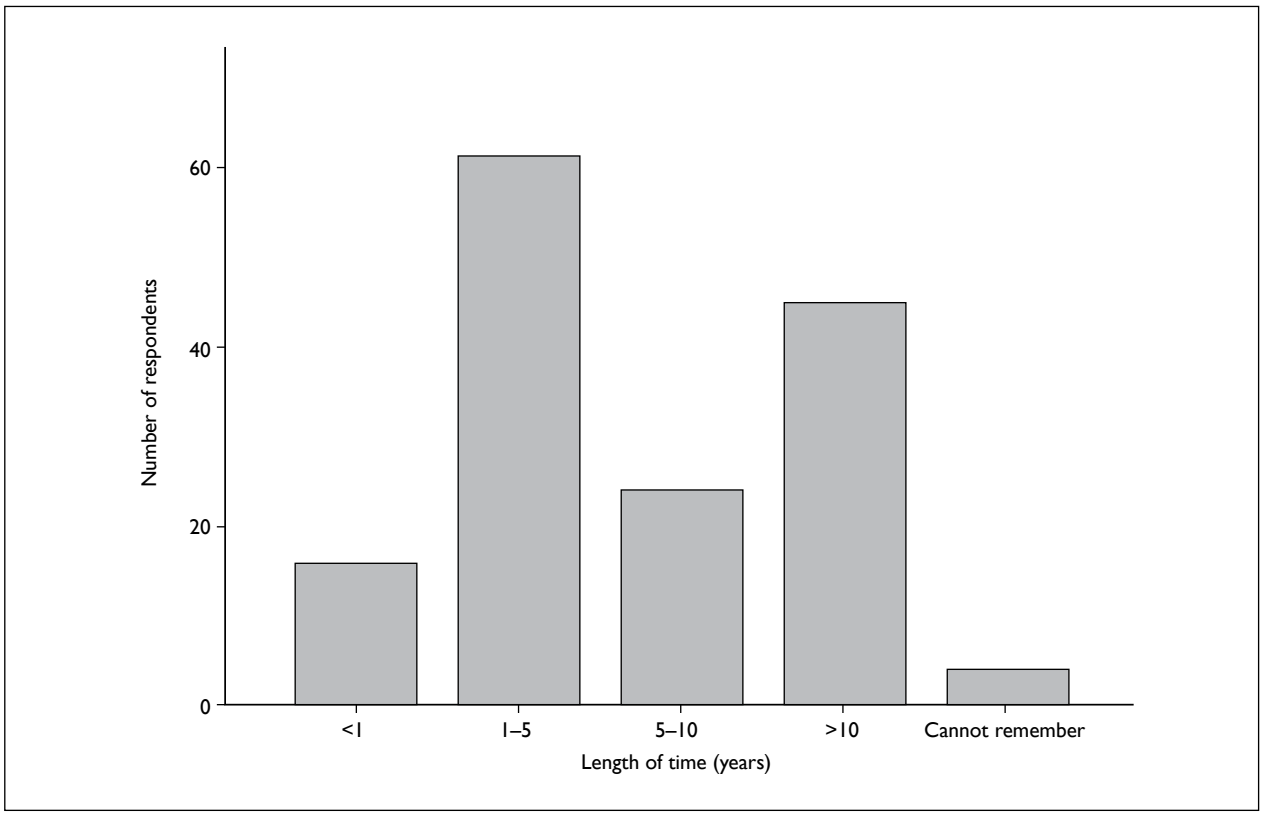


FIGURE 11 *Number of years taking prescribed laxatives.*

for bowel movements, it suggests that the laxative regimes in our sample were working in terms of frequency and approximately one-third of our sample were achieving the wish not to strain at stool.

Participant-defined 'successfully managed constipation'

The results of this question broadly reiterated what people wanted to achieve by taking a laxative, i.e. successfully managed constipation would mean ease, frequency, regularity and soft consistency of stools. However, only 10% of respondents to this question said that successfully managed constipation would mean 'without the use of laxatives'. This finding again reiterates belief that managing constipation without a laxative is not a priority for many people.

Postal questionnaire follow-up response rates

The self-completion questionnaire was sent at three time points (3, 6 and 12 months). At 3 months the response rate was 80%; at both 6 and 12 months it was 85%. This suggests that, despite length of the questionnaire, the time taken to complete it and the added burden of the daily diary at the first two time points, respondent fatigue was not an issue.

Daily diary

The daily diary that we used in LIFELAX had been developed during the qualitative study that accompanied the set-up of the STOOL Trial.[19] The diary method was chosen in a bid to minimise recall bias. Data on bowel habits and symptoms based on the Rome II criteria[122] were gathered in a structured way (tick box format), completed daily and returned each month for 6 months. In addition to these data, the diary collected information on adverse events, relapse rates, use of laxatives, costs of food purchased or activities undertaken as part of any diet or lifestyle changes made; and any out-of-pocket expenses associated with constipation and its management.

Although previous experiences of diaries in studies with older people suggested that 90% of diaries

would be returned completed,[132,133] we could find no evidence that a diary such as this had been used to collect data on bowel function/health and associated costs on a daily basis for such a length of time.

The greatest number of diaries was returned in round one, and the response rate was approximately 73%. In subsequent rounds there was a slight decrease in response rates (*Table 14*). The overall response rate to the diaries was 64%.

While these response rates were not of the magnitude of those in the previous studies cited above, we would not go as far as to say that as a data collection tool a daily diary of this sort for this population was inappropriate.

Anecdotal evidence from telephone conversations with participants suggests that there was sometimes a concern that they were just saying the same thing every day, or that nothing had changed, so there was nothing new to report and therefore a perception that it was not necessary to fill in the diary and send it back. Cognisant of this, we would recommend that any researchers contemplating using such a tool consider clearer instructions to participants regarding the importance of completing the diary even when they think that they have nothing of interest to report, and perhaps make use of regular reminders to encourage completion and return.

We also know from telephone calls to the LIFELAX office that some participants found the diary burdensome to complete. Given its physical size, the sensitivity of the subject area (a few respondents remarked that the diary was not something they wished to have on public view, so kept it in the bathroom or toilet), and the duration of the task, this sentiment was not entirely unexpected. As highlighted in the CONSORT diagram (see Chapter 4, *Figure 7*) we encountered a complex withdrawal pattern, with a number of participants partially withdrawing and selecting which assessment tools they would continue to complete. We had several participants electing to continue to receive the postal questionnaires and/or telephone interviews but not the diary.

Item response rates

Analyses of the item response rates suggest that the daily diary contents were not troublesome to participants.

Each day participants were asked to record the number of bowel movements during that day. This question was fully answered (i.e. a response on every day in the diary) in over 88% of diaries. In the remainder it was partially answered (i.e. a response was recorded, but not on every day). This suggests that the diary may be a useful way of collecting such data.

The items taken from the Rome II criteria (straining, hard/lumpy stool, incomplete evacuation, stool not passed and digital evacuation) were completed in full on 97% of occasions.

The item response completion rate was of a similarly high percentage for the items dealing with taking medication for constipation prescribed by the GP, bought OTC or any other measures taken to relieve constipation.

TABLE 14 *Diary response rates for the LIFELAX daily diary over six rounds*

Diary number	Number returned	Response rate[a] (%)
1	112	73
2	109	70
3	103	66
4	93	60
5	90	58
6	84	55
Total	***591***	***64***

a As the levels of withdrawal and partial withdrawal were complex, we elected to use $n = 154$ (the total number of participants consented and eligible to complete a round 1 diary) as the denominator for all these calculations.

These data would suggest that the individual items within the diary used to collect information about bowel function and medication were not burdensome to complete, and that a diary is a satisfactory way of gathering them. However, the duration over which the diaries needed to be kept and the daily repetition may have led some participants to withdrawing from this aspect of the study.

Table 15 reports the estimated effects on our primary outcome measure (patient-reported QoL); however, we must stress that we feel that the interval estimates are too wide to be of very much use. In reporting them, if so desired, they can be entered into a meta-analysis. We do not believe the data collected would merit further analysis, but they will be banked. Should any future meta-analysis be undertaken we will share then with the investigator and they can decide whether to include them.

Economic evaluation

Resource usage and costs

Information was collected about visits to a general practice, visits to hospital and telephone consultations between the start of the intervention, and at 3 months post intervention. The total resource use across each arm is shown in *Table 16*.

The main comparison of interest was between the control arm and the two intervention arms, so common costs were ignored as they do not affect the choice between interventions.[211] Information collected on the use of health-care resources was strictly in connection with the condition being studied. *Table 17* shows the unit cost data that were used to calculate results in *Table 19*.

The mean per-case recorded costs for the intervention and control arms over 3 months were similar, and are shown in *Table 18*.

TABLE 15 *Estimated effect of the interventions on the primary outcome measures*

Time (months)	Comparison of intervention			
	Personalised vs control		Standardised vs control	
	Mean	95% CI	Mean	95% CI
PAC-QOL overall score[a]				
3	0.08	−0.19 to 0.36	0.14	−0.09 to 0.37
6	−0.11	−0.41 to 0.20	0.04	−0.19 to 0.27
12	−0.09	−0.38 to 0.21	−0.04	−0.32 to 0.23
PAC-SYM global score[b]				
3	0.10	−0.25 to 0.45	−0.00	−0.25 to 0.24
6	−0.27	−0.72 to 0.18	−0.17	−0.50 to 0.17
12	−0.08	−0.47 to 0.30	0.18	−0.20 to 0.56

CI, confidence interval.
a At baseline the overall mean and SD of the PAQ-QOL overall score were 1.30 and 0.77, respectively.
b At baseline the overall mean and SD of the PAQ-SYM global score were 1.10 and 0.79, respectively.
The difference at each of the three time points was obtained by comparing each of the groups that received an active intervention with patients in the control group. Baseline scores were included as a covariate; variation between practices was included as a random effect. Models were fitted using the 'xtreg' procedure in STATA 8.

TABLE 16 *Total resources utilised by all trial participants by arm*

Arm	Control	Personalised	Standard
GP visit	26 out of 27	12 out of 13	40 out of 42
Outpatient	2 out of 27	0 out of 13	1 out of 42
Telephone GP	0 out of 27	1 out of 13	2 out of 42
Telehone practice nurse	0 out of 27	1 out of 13	2 out of 42

TABLE 17 *Resource costs for non-common items*

Item	Cost 2007–8 (£)	Source
Outpatient hospital visit	193	2007–8 payment by result tariff for an outpatient gastroenterology, first visit (£95 if second visits)[a]
General practice visit	34	£31, 2006–7 PSSRU,[b] 3.5% inflator per annum
Telephone consultation: practice nurse	9	£8, 2006–7. PSSRU,[b] 3.5% inflator per annum
Telephone consultation: GP	21	£24, 2006–7. PSSRU,[b] 3.5% inflator per annum

a www.dh.gov.uk/en/Managingyourorganisation/Financeandplanning/NHSFinancialReforms/DH_077279
b PSSRU Unit Costs of Health and Social Care 2007; www.pssru.ac.uk/pdf/uc2004/uc2007.pdf

TABLE 18 *Mean costs per case in each trial arm*

Arm	Mean costs (£)
Control	47.04
Personalised	33.69
Standardised	38.40

The amount of data collected about resource use was sparse due to the low number of respondents. In the 3 months of follow-up, there were two hospital visits for the control group, one telephone consultation with a GP, and one with a practice nurse for the personalised arm; and one hospital visit, one telephone consultation with a GP and one with a practice nurse for the standardised arm.

Table 19 shows that differences were found for the personalised arm in hospital visits and telephone consultations. For the standardised arm these differences were also found. These differences are based on resource use of a small numbers of cases in each arm and care should be taken if using these findings for predicting changes in service use.

TABLE 19 *Significant reductions in probability of resource category use at 3 months*

	Difference (%)	
Arm	Hospital visits	Telephone consultations: GP and practice nurse
Personalised	−0.074	0.077
Standardised	−0.050	0.071

Negative numbers represent a decrease in probability of using resource compared with control.

Across both intervention arms there had been a relative reduction in hospital visits at 3 months and a relative increase in the use of telephone consultations. For the personalised arm there was a 7.4% decrease in hospital visits and there was a 5% decrease for the standardised arm. For telephone consultations the personalised arm is associated with a 7.7% increase, compared to the control group, and the standardised arm is associated with a 7.1% increase. *Table 20* shows that these differences translate to a small reduction in hospital costs for the intervention arms compared to the control arm and a smaller increase in telephone consultation costs.

The estimated savings in NHS costs are £13.34 for the personalised arm and £8.63 for the standardised arm.

TABLE 20 *Costs savings (increases) in treatment arms compared to control at 3 months*

	Mean difference (£)
Personalised	
GP visit	1.36
Outpatient	14.30
Telephone GP	(1.62)
Telephone practice nurse	(0.69)
Total	*13.34*
Standardised	
GP visit	0.36
Outpatient	9.70
Telephone GP	(1.00)
Telephone practice nurse	(0.43)
Total	*8.63*

Figures in parentheses represent increased costs compared with the control arm.

Patient costs

Ideally, the above would be supplemented by costs incurred by patients while accessing NHS care. However, the participants supplied insufficient information for these to be computed.

Summary

In describing the participants in LIFELAX we are confident that the mean PAC-SYM and PAC-QOL scores at baseline suggest that our sample did not experience extreme symptoms or impact upon QoL. The mean scores on the HADS show there was no evidence of anxiety or depression either in the group as a whole or arm by arm.

Only a very small minority (7%) of participants fell outside the range for normal frequency of bowel movement. However, this frequency was not necessarily satisfactory to our participants.

In our sample over 30% of respondents had been taking a prescription laxative for 10 years or longer and 15% of the respondents had taken an OTC laxative for 10 years or more. This reinforces the chronic nature of the condition.

Item response rates suggest that the items within the diary used to collect information about bowel function and medication were not burdensome to complete and that a diary is a satisfactory way of gathering them. However, the number of diaries and the daily repetition may have led some participants to withdrawing from this aspect of the study.

Due to the quality and quantity of data collected we are reluctant to draw any firm conclusions as to the effectiveness of the intervention.

Regarding the economic evaluation, the recorded related health-care costs show a cost saving of £13.34 (£47.04–£33.69) for those in the personalised arm compared with the control arm, and a smaller saving of £8.63 (£47.04–£38.40) for the standardised arm. These savings occurred because of reduced hospital costs, offset by a smaller increase in costs incurred through additional telephone consultations. As there was no significant change measured in utility, cost minimisation would suggest that the personalised arm would be the preferred course, as it produced the greatest cost savings. This finding is qualified by the fact that the reduction in health-care costs was due to a relative small number of cases in a relatively small sample.

Effects on HRQoL

Baseline characteristics

Health-related quality-of-life data were collected from the trial participants at baseline (before the commencement of the arm appropriate intervention) and at 3 months (primary end point). HRQoL was measured using the EQ-5D,[212] with 89 participants providing data at both time points. The EQ-5D is designed to be administered in the form of a self-completed questionnaire. Respondents are asked to define their own health state in terms of the five dimensions (mobility, self-care, usual activities, pain/discomfort, anxiety/depression) and their level (no problems, some/moderate problems/extreme problems) for each of the dimensions by ticking which statement applies for each dimension (see Appendix 4). EQ-5D is used to determine a utility value between 0 and 1, with '0' representing death and '1' perfect health.

The mean utility,[213] at baseline, of the personalised intervention arm was lower than that of the control arm, as shown in *Table 21*.

TABLE 21 *Mean utility at baseline of trial arms, and comparison of mean utility of intervention arms with control arm*

Arm	Mean utility	SD	*n*
Control	0.714	0.231	29
Personalised	0.536	0.307	16
Standardised	0.711	0.269	44

SD, standard deviation.

Within-arm differences

Table 22, shows that all arms experienced a reduction over the a 3-month period. The largest reduction in utility scores was experienced by the control arm, the smallest reduction by the personalised arm.

Between-arm differences

Table 23 shows the change in mean utility of each of the treatment arms compared with the change in the control arm. The effect of both the personalised and standardised intervention arms was to relatively increase the utility or lessen the absolute reduction; the standardised arm having the greater effect and experiencing the smallest reduction in utility.

TABLE 22 *Within-arm differences in mean utility between baseline and 3 months of trial arms*

	Baseline		3 months		
Arm	**Mean**	**SD**	**Mean**	**SD**	***n***
Control	0.714	0.232	0.680	0.305	29
Personalised	0.536	0.307	0.523	0.300	16
Standardised	0.711	0.268	0.686	0.288	44

SD, standard deviation.

TABLE 23 *Differences in utility between control arm and intervention arms between baseline and 3 months*

Arm	Difference in mean	Variance pooled
Personalised	0.02	0.04
Standardised	0.01	0.04

Summary

All of the trial arms experienced a reduction in utility, as measured by EQ-5D.

Chapter 6

Results: the process evaluation

Introduction

Within the LIFELAX trial the process evaluation provided a unique opportunity to investigate the stages of development and implementation of an RCT in 'real time' as events occurred. We observed that the trial team's activities centred on two key 'technologies'. The first was the development of the RCT itself, which – in common with other forms of research – required the investment of expertise, finance, clinical and bureaucratic support, and the sustained collaboration of a number of contributors. The second technology at stake was the development of training packages and materials for the diet and lifestyle interventions, and subsequent deployment of this training by the trial team, in particular the research dietitian and nutritionist, to an audience of practice nurses. The research dietitian and nutritionist delivered the training packages with the intention that the nurses would later deploy target skills and materials with patients in the practice. An important observation was that the underlying factors that supported each technology differed, such that while the trial team were able to overcome a number of barriers to the deployment of the RCT, many of the factors influencing the nurses' reception of the training packages were beyond the trial team's control.

In the first section of the chapter we discuss the key barriers that taxed the implementation of the RCT, and the trial team's efforts to implement the trial in primary care practices. At the time of LIFELAX, the organisations on which the trial depended were in a stage of transition with regard to their interpretation of Research Management and Governance (RM&G) guidelines. Consequently, there was some ambiguity across these organisations about how the RM&G guidelines should be implemented and this had a number of effects on the trial team's capacity to deploy the trial. In particular, the trial team received different instructions across PCTs regarding how the trial should be implemented. In most cases practices contemplating involvement in the trial were faced with the prospect of additional work on behalf of the trial team. In this regard, the LIFELAX RCT – in common with almost all forms of research – did not offer an immediate advantage to primary care practices. Indeed, quite the reverse was true. In this context, the trial team worked hard to find innovative solutions to potential barriers and reduce the amount of work required of NHS staff, while maximising the attractiveness of the research topic and experimental interventions. These issues, and the approach adopted by the trial team, have been described in more detail in Chapter 4, specifically with regard to assessing strategies against those proposed in the STEPS report,[193] and other literature.[194] We draw primarily on interview data to describe the 'technology of the RCT', as transcripts of the trial team meetings provide a less concise and at times less explicit account of key issues. (In LIFELAX trial team meetings, many problems associated with RM&G guidelines or MREC decisions emerged over successive meetings. The trial team shared some understanding of the history of RM&G guidelines and MREC stipulations, and therefore the contexts underpinning particular problems were not always made explicit. In interviews, however, these issues were articulated overtly and unambiguously by the interviewees as they attempted to inform the ethnographer.)

In the latter half of the chapter we describe the 'second technology' of LIFELAX, namely the development and deployment of training packages for practice nurses. In the first instance, the trial team developed a training package in BCC techniques, and the production of diet and lifestyle materials (information sheets, a video and behaviour change manual). The second activity was the delivery of BCC training by the research dietitian and nutritionist to nurses in the BCC arm of the trial. The intention of the trial team was that the nurses receiving training in BCC would then deploy these skills with recruited participants in their own practice. Due to the pragmatic design of the trial, the interactions between the nurses and participants were unobserved by the trial team. In this chapter, we describe the perceived utility and reported use of the BCC materials and training through the accounts of practice nurses, GPs and practice managers enrolled in the trial. The reports from primary care staff suggested that the topic of the trial was not seen as a clinical

priority when considered alongside targets identified in the GMS contract, and that diet and lifestyle approaches were informally considered part of the current skill set and training of practice nurses. In attempting to find meaning in the trial's interventions, the practice nurses suggested that community nurses might benefit from the BCC techniques, as these staff were viewed as being more likely to work with patients suffering chronic constipation. Finally, we report how the interventions were perceived by participants through their interactions with enrolled nurses.

Technology of the RCT: bureaucratic work and the organisation of resources

The specific difficulties encountered by the trial team in meeting the requirements of the MREC and local governance bodies have been reported earlier in this report (primarily in Chapter 4). Consequently, we do not reiterate them in detail here. Nevertheless, we describe the overarching structural constraints that consumed much of the trial teams' resources through the course of the research, and the key role of social networking in surmounting these barriers.

The LIFELAX RCT was set in primary care, where a number of organisations shaped the possibilities of the research. In particular, the trial protocol was required to be flexible enough to meet the requirements of various sites (general practices) and governing bodies (PCTs, the MREC, LRECs), while maintaining the scientific rigour of the RCT. In the opening phases of the RCT, the trial team's activities were focused on the identification of relevant stakeholders, meeting the requests of regulatory bodies, negotiating the cooperation of organisational networks, procuring resources from these networks, and arranging access and integration in busy clinical environments. The sequence of work followed a trajectory set out by the RM&G framework for clinical trials in the UK.[214] However, some of these milestones proved to be difficult for the trial team to reach in practice. In particular, at the time of the trial, RM&G guidelines were under a process of continuous development, with a number of official documents being issued throughout the life of the trial and changes in policy, expectations and practice emerging over this period. This climate contributed to localised and sometimes stringent interpretation of the RM&G guidelines by different governance bodies. Consequently, both the LIFELAX and STOOL trial teams struggled to fit the design and conduct of their respective RCTs to RM&G requests across PCT sites.[19] As demonstrated by a growing number of reports in the literature (e.g. Wald[215]), the LIFELAX and STOOL trial teams were not alone in experiencing these difficulties. During the initial implementation of the LIFELAX RCT, the trial team encountered substantial difficulties in their attempt to meet the requirements of their MREC, and in particular, its request for SSAs. If the trial team had attempted to obtain SSAs at the level of individual general practice sites, recruitment may have been severely hampered. However, the trial team negotiated a workable solution by naming the head of a local PCRN as PI for the region.[216] SSAs for all practices within the domain of the research network were then obtained through the credentials of this one key individual. Although this strategy was effective in speeding administration for the trial and improving the possibility of successful practice recruitment, it required ad hoc problem-solving and negotiation on the part of the trial team. Responding to an article published in the *British Medical Journal*[215] decrying the bureaucratic, seemingly obstructive process of seeking MREC/COREC approval, the trial manager explained how this strategy was developed for LIFELAX:[216] 'A casual remark from an LREC secretary, during another telephone conversation, about two or more sites "working together" opened up another possibility. I could try and find out whether practices would collaborate and therefore have one PI assuming responsibility for more than one site'.

The solution for the trial team was thus organised through informal networking and circumstantial conversation. Moreover, within the MREC there appeared – through access to several e-mails – to be a lack of agreement regarding what constituted 'high risk' to patients, and how workable solutions should be arranged, and a cautious approach was specified. In the execution of the LIFELAX trial, issues surrounding the interpretation of ethics and research governance placed a great deal of pressure on the trial team to continually develop creative and workable solutions. However, it is unclear to what extent these issues stemmed from the unsettled climate at the time of the LIFELAX trial, and what were more generic issues. Unfortunately, in the process evaluation we did not interview or otherwise investigate the perspective of the MREC or other governance bodies. Therefore, our report is based on the observed and reported experiences of the trial team, practice staff and participating patients.

The progression of the LIFELAX trial depended on cooperation between the trial team and key individuals from a number of external organisations. To facilitate the allocation of resources and other administrative tasks, the trial manager actively pursued external contacts and developed working relationships through a sequence of telephone calls, written communication, site visits and social gatherings, some of which occurred in 'out of hours' time. In this regard the trial relied heavily upon the social networks constructed and maintained by the trial manager to achieve various milestones. Social aptitude was a vital component of the trial manager's repertoire, especially when teamed with skills more overtly recognised as desirable in the research context: such as those based on organisation, procedure and methodological rigour. *Box 1* presents an abbreviated extract from a meeting in which the trial manager's role in securing funding is explicitly recognised.

The extract in *Box 1* provides some useful information regarding the imperative of social networking. Given the very slow rate of recruitment observed in a sister trial (STOOL[19]), NHS SfS funding was perceived as being crucial – 'very attractive indeed' – for the successful recruitment of practices into LIFELAX. Although the necessary step of 'filling in … forms' to secure this funding was mentioned by the CI, flexibility and responsiveness in the bureaucratic system was ascribed to personal interaction; in this case the 'super duper relationship' formed between the trial manager and 'Jane' (a DH Research and Development Manager).

The trial team worked within MREC guidelines regarding methods of recruitment. In particular, the trial's design was shaped by an MREC ruling that the trial team could not directly access patient information or make direct contact with patients, but instead needed to work 'through' general practice staff. Consequently, much of the work of identifying, contacting and processing eligible patients was assigned to practice nurses. After experiencing a slow recruitment of practices, the trial manager reassessed the work asked of these staff, and proposed a new process. This was designed to simplify work by integrating it more fully into routine procedures, in accord with principles set out in the STEPS framework.[193] Essentially, the trial manager discovered, through discussion with practice representatives, that

BOX 1 *Social aptitude as a key component of trial management*

> *Chief investigator*: now the support for science funding and many, many, many thanks and congratulations in particular to [the trial manager], also to [trial manager 2] for filling in these forms and for [the trial manager] *developing a super duper relationship* with Jane [a science funding administrator] … erm but er, the bottom line is we have got the support for science funding so we will be able to offer practices a per patient recruited amount of approximately £60, … So [in summary] I think that's going to be *very attractive indeed* to the practices erm, *you and Jane and Claire* [a second administrator] are still sorting out the nitty gritty for the administration
>
> *Trial manager*: Indeed yes, the, Jane made some requests and we weren't quite sure what the requests actually meant so I contacted Claire … Jane has been out until today and won't be back until later this afternoon so [I'm] just *working between the two of them*
>
> (Trial project meeting, 24 May 2004; authors' emphasis, p. 6)

BOX 2 *Restructuring recruitment procedures to reflect 'routine practice'*

> *Trial manager*: … we haven't been able to recruit the number of practices and that has implications for recruitment of patients … *it's this level of work* that we are expecting [practices] to do for us that's the sticking point and that's what we have got to work around … [in particular] I have a concern about practices writing to patients with this appointment for a clinic, and I thought well *it's a pragmatic trial*, and we need to really do things as they would happen *in the real world*, … if [the practices'] local custom is to ring patients to invite them [to talk] about their condition why are we insisting that they have to write to patients, that's not what they would routinely do, and *the whole point of this trial* is that it maps onto *routine practice life*, as much as it possibly can. So I thought well we could always suggest an amendment to the protocol allowing GP's and nurses and receptionists to ring patients …
>
> (Interview II, trial manager, authors' emphasis, pp. 1–4)

'normal' (i.e. non-trial) invitations for patient appointments weren't made on paper, but rather were initiated by a telephone call. This new means of patient contact was built into the amended recruitment process. The new process also fitted closely with the pragmatic design of the trial, which emphasised a 'naturalistic' application of trial procedures. *Box 2* presents an extract of an interview in which the trial manager outlined the rationale for his plan.

The trial manager's account serves two purposes: demonstrating both personal enthusiasm and commitment to the trial, and an attempt to find a workable solution despite the limitation of having no direct access to patient details. In this instance the suggested course of action was to integrate trial work with existing patterns of activity in primary care settings. Nevertheless, the MREC reached the decision that the planned approach was unworkable on the basis that telephoning patients at home would constitute a form of harassment. The MREC decision also prevented recruited practices from telephoning patients to check if they had received an information letter or to see if the patient wanted to reschedule an appointment for the trial. This combination of barriers, in addition to those cited earlier in this chapter, contributed to a growing level of frustration within the trial team. *Box 3* presents an extract from an interview with the trial's CI in which she explained her assessment of the current climate of research governance.

The CI began her account by describing what she perceived as an 'overinterpretation' of RM&G and ethical principals by localised administrators and MRECs, respectively. Two effects of this bureaucratisation were identified: the process of research was stalled, '[held] up', and more significantly an 'unethical' consequence was manifest through patients being denied the benefits of clinical research (either through participation in a research study or benefitting from evidence-based care). The CI also offered a description of the roles and responsibilities implicit in the deployment of clinical trials. In particular, she described fundamental differences between the work of three groups of actors: administrators, researchers and clinicians. Researchers, in the context of a pragmatic RCT, were described as having an understanding of the 'grass roots' issues of clinical practice with regards to research involvement. In particular, researchers were described as being aware that clinicians were unlikely to invest resources in purely research-based activities without significant incentives. Conversely, administrators were not 'understand[ing] the realities' of what was needed 'to make things work' in the context of primary care research. Thus the problem was identified as one of governance, and not the (mis)translation of research priorities to clinical practice. The CI's account is underpinned by a powerful discourse of ethics and pragmatics: the trial team are identified as being qualified to deploy a sound clinical trial, while governance administrators risk generating 'unethical' practice through an overly cautious

BOX 3 *Frustration with the Research Governance Framework*

Chief investigator: Erm, I think initially there were very significant barriers … and also considerable delays in getting trust R&D approval sorted out for the [the trial], and I, you know, fully appreciate the need for … the research governance framework … but I think there has been *overinterpretation* of some of the stipulations and the requirements to the extent that it *holds up research* and I am thinking here not just of the experience with [the current trial] but with various other studies … since the research governance framework came into being erm, I think that its swung so far the other way now that people are being so ultracautious that there is a danger of research that is potentially beneficial to patients not actually being undertaken and in my opinion *that's as unethical as doing poor research* and research that's potentially detrimental to patients.

… I also think that some of the restrictions and the stipulations and the things that people in ethics committees and in trust R&D offices are asking for are probably symptoms of … [them being] primarily administrators and actually [they] have never done hands-on research themselves and don't understand the realities of what its like doing research and the approaches that one needs to take to make things work so er, so for example the whole notion that in the interests of patient confidentiality, you know that we would all respect, that you have to have this kind of two stage approach to patients and that their names cannot possibly be released in any way to the research team until the patient has given their consent I think that shows perhaps a lack of understanding of barriers for busy practitioners, those very barriers that [the trial manager] has been talking about all along; that really practices don't have the time and the resource to write out to patients, get them in, go through the whole process of explaining the study to them

(Interview, CI, authors' emphasis, pp. 1–2)

approach and seemingly arbitrary variations in judgement.

The issues affecting the successful deployment of LIFELAX and its sister trial STOOL were recounted by a senior member of the trial team (Senior Researcher 2 – SR2) in an interview, an excerpt of which is presented in *Box 4*.

In *Box 4*, SR2 describes a problematic intersection between: (1) an evolving research governance framework; (2) the agenda of academic researchers; and (3) the concerns of primary care. In the first paragraph SR2 describes a change in the way ethics committees and research governance bodies have responded to research, citing escalating bureaucratic procedures that are not matched to the potential risks posed to participants. The quote contains a description of how research may have been conducted prior to changes in the research governance framework over '… the last 3–4 years'. Specifically, where studies posed little clinical risk to patients, researchers were able to deliver recruitment information that was tailored to this low level of risk and to the research design, keeping technical information to a minimum where appropriate, and thus making the process of consent 'straightforward' for both patients and researchers. However, SR2 explains that recent research governance stipulations universally require a more complex approach to consent, often involving the input of clinical staff. Therefore, although originally the research team 'would do everything' in the research process, the burden of patient recruitment in primary care has now passed to practice staff. SR2 adds a qualifying statement to his criticism of research governance, by identifying the '… *need* [of ethics/governance frameworks] *to operate*' in matters where patient wellbeing is in question. Finally, SR2 summarises that the key concern is an increase in the *undiscerning* application of research governance stipulations in an uncritical and generally uniform manner across research studies. This approach requires, at times, unnecessarily complex recruitment procedures, greater input from clinicians, and correspondingly affords the trial team less control over the delicate recruitment process.

In the second paragraph of *Box 4*, SR2 explains why greater involvement of clinicians in the recruitment process is problematic. Specifically, the agenda of GPs and other primary care staff is shaped by the changing General Medical Services (GMS) contract. While researchers have the enthusiasm, resources and interest in implementing their own research projects, primary care staff are '… very very busy' and have '… other priorities'. These priorities it is argued do not

BOX 4 *Different priorities in research practice: research governance, researchers and primary care*

Senior researcher 2: … I think the real barriers are in primary care and this is where the situations have changed over the last 3–4 years with research governance framework so in the past doing the trial in primary care, you would make sure that having got agreement from the primary care team that they would allow their patients to participate in the trial, and the research team would do everything else … Er the consent form would be straight forward 'I am willing to participate in the trial or I am not', its … something which doesn't have any major impacts on your life, you know, … its not a, a dangerous drug, its not a dangerous procedure, its nothing life threatening its just 'will you participate in the research'. So the procedures were much more tailored to the severity of the risk is my view and … you know if I had been doing a study of heart transplants then clearly we would not have been using the same procedure then, then the procedure would be much closer to the way ethics committees and research governance need to operate, there would be a much fuller explanation by the consultants, exactly what it involved, etc., so it's about matching risk to er bureaucracy

… you see it's the enthusiasm of the researchers, … the focus of the research team that this is the only thing which is important to them, enables you to build a rapport with the participants, ensure they understand fully what's going on, explain it to them, er and so that they are quite clear that it has no detrimental effect on their outcomes, etc. What you have got now though is a very very busy primary care and I no way am going to lambaste or criticise primary care, you've got very very busy primary care, these individuals have other priorities which are at the moment far worse than they probably were 5 years ago too, because of the new GP contract so primary care contracts have changed so that they are having to meet all these prevention targets making sure everybody, plenty of people have had flu vaccines with the number of kids out there who have been coughing all those things have to be met. So their work load is substantially more than it was say 5 years ago, life is far more complex, there is big business here, [a] division of labour, and none of the individuals involved have … anywhere near the same kind of commitment to the project as you or I do, as researchers, so no wonder the enthusiasm is not there for recruitment. So the barriers are not you know primary care, the barriers are about the way that research has to be done because of research governance so I think that's the biggest barrier

(Interview: SR2, 22 April 2005, authors' emphasis, pp. 2–3)

always overlap with those of research. Therefore the enforced transition of control over recruitment – from dedicated researchers to busy clinicians – is counterproductive. SR2 reiterates that the central problems to implementing research are not to be found in primary care, but in '… the way that research has to be done because of research governance'.

The LIFELAX RCT required bureaucratic approval and coordination across a range of organisations, including those concerned with ethics, administration, finance and human resources. Congruence between relevant networks was sustained by the social, largely *hidden work* of the trial manager in identifying, creating and maintaining relationships, with key individuals in relevant positions of authority in these organisations. Subsequently, in order for the trial to progress and meet milestones, the trial team had to rely on non-standardised and previously unreported methods. Although the trial team worked hard to promote the RCT and to enhance recruitment, the research was hampered by three key features of an 'unstable research governance environment', namely: (1) differences in interpretation and implementation of RM&G guidance across administering bodies; (2) an interpretation of RM&G guidance by PCTs, and ethical decisions by the MREC, that was viewed as 'overcautious' by senior research staff; and (3) by the trial team's limited access to patient data and contact procedures as stipulated by the MREC. Reasons for particular interpretations of research governance and ethics, and disparities in interpretation, require further investigation. Notably the process evaluation did not include a detailed investigation of the perspectives of the MREC – other than via available e-mail correspondence and letters – or the views of PCT officials. However, an endemic fear of litigation in light of the incidents at Alder Hey, and more recently Northwick Park Hospital, may be a contributing factor to the 'cautious' approach of the MREC and PCTs, as perceived by the trial team.

A summary of the findings from observation of the trial team at work is presented in *Table 24*.

The 'second technology' of the LIFELAX trial: training packages for practice nurses

Studies investigating patients, their data or the work practices and systems implicated in their care often rely on the cooperation and commitment of medical staff. However, factors that affect the attractiveness of research participation for clinicians in various settings are multiple and poorly understood.[217–219] Moreover, given the level of commitment required of clinicians, it is perhaps not surprising that poor recruitment of this group to RCTs is an established subject within the literature.[220] Subsequently, in the LIFELAX trial, the research team attempted to maximise the attractiveness of the study by promoting its applicability for primary care medicine, following strategies set out in published research.[193,194] In particular, the introductory materials and presentations to practice staff emphasised the potential benefits of reducing laxative prescriptions, decreasing patient contacts and upskilling staff, by equipping them with transferable skills in patient education and delivery of lifestyle advice. Nevertheless, despite some initial expressions of interest, the trial team found it difficult to secure the commitment of practice managers and senior partners. While some of the barriers to practice recruitment have already been described in this report, additional

TABLE 24 *Barriers to the integration of the RCT in primary care*

The trial team were primarily engaged in meeting administrative and practical objectives and completing ancillary paperwork. However, the RCT relies heavily on cooperative networks. Cooperation (*congruence)* between networks was sustained by the social – and largely 'hidden' – work of the trial manager in identifying, creating and maintaining relationships with key individuals in various organisations
Due to differences in the application of RM&G guidelines across sites, and interpretations of the guidelines that were not 'research friendly', the trial team were under pressure to continually develop creative and workable solutions to emerging practical problems. This formed a barrier to the satisfactory and timely achievement (*disposal*) of essential milestones in the delivery of the trial
The MREC ruled that the trial team could not directly access patient information. Consequently, much of the work of identifying, contacting and processing eligible patients was assigned to practice nurses. As practice staff were often busy, the recruitment process was initially very slow
Additional barriers to the trial included a research topic that did not match the clinical priorities established through a new GMS contract and numerous problems in acquiring RM&G approval, such as a slow response from some PCTs, out-of-date application procedures and 'broken' or old web resources

– less readily apparent – concerns overlaid these practical obstacles. In particular, the nursing staff appeared to be unenthused by various aspects of the research. Nurses interviewed in the BCC arm of the trial described the counselling techniques as being familiar, or as one nurse commented; '… the information [was] … given to experienced health-care professionals; it wasn't something we were unfamiliar with' (Nurse 4, interview, 11 October 2004). Most of the nurses across all three arms of the trial described chronic constipation as a comparatively 'uninteresting' topic, and an issue that seldom arose in their routine encounters with patients. Consequently, interest in both the topic of the trial and the experimental interventions was low. In this section of the chapter we describe feedback from a range of practice staff regarding their perception of the research topic, and the role of practice nurses in implementing the LIFELAX RCT.

Barriers and facilitators to normalisation of the LIFELAX nurse training packages

Through the nurses' accounts it is possible to identity two features of the training packages that were salient to them. The first was the central topic of the trial – chronic constipation, perceived by most respondents as a problem not routinely encountered by practice nurses in their interactions with patients. In this regard the LIFELAX trial was perceived by most of the nurses as presenting them with an additional clinical responsibility. In particular, chronic constipation was regarded as an issue that was typically managed fairly successfully by laxatives and that was typically within the remit of care delivered by other professionals (GPs, community nurses). The second issue for nurses in the personalised arm of the trial, were the BCC techniques. The nurses who received instruction in BCC described the training package as not offering new skills, but rather reinforcing current approaches. Nurses in both personalised and standardised advice arms of the trial reported the diet and lifestyle materials as having some relevance to their standard practice (for conditions such as obesity and healthy living). However, these comments were made in the context of a generally negative report of trial involvement, and it is not possible to determine how or if these materials would be used beyond the life of the research.

When presented with resource-intensive work that is poorly defined – such as the management of some chronic conditions – medical professions may attempt to divert responsibility for the condition to another closely aligned professional group (e.g. Viner[221]). Across the interviews with practice nurses, chronic constipation was described as falling outside the *boundaries* of their routine work, and as a responsibility *distributed* across community nursing teams and GPs. *Box 5* presents a more detailed explanation through the independent accounts of two nurses.

Nurse 9 explained that the topic central to the trial's interventions – chronic constipation – was not a key feature of practice nursing. Specifically, she identified the condition as a concern '*for the doctor*' or '*nurse practitioner*'. In this regard, Nurse 9 viewed the topic of the research – and by extension the training packages – as having little direct relevance to her day-to-day work. In the second account, Nurse 4 echoed this interpretation. In particular, she explained clearly that the

BOX 5 *Defining roles: the appropriateness of 'constipation work' for practice nurses*

Interviewer: … did you find [the research consultation] differed from how you would normally interact with those patients or –

Nurse 9: Ah yes I would say so because I don't, I mean unless we are doing a medication review with patients who are already on lactulose or the, whatever medication, then we probably wouldn't; it's not a question [chronic constipation] that ever comes up unless people are coming in, and I mean they *wouldn't come [in to see] the practice nurse* anyway, to discuss that, if they had any problems they would come in to see *the doctor* or the *nurse practitioner*. So it's not a subject that ever comes up really

(Interview: nurse 9, brief intervention, authors' emphasis, p. 2)

Also:

Nurse 4: I don't specifically counsel people about the their bowel habits, erm it doesn't tend to come into *my role* … I don't get involved in it other than I give healthy eating advice, erm in the process of a lot of other consultations that are just a part of it, well-woman, well-man checks, we always give dietary *advice* we always give exercise *advice* … I think maybe *the district nurses* have a lot more to do with [chronic constipation in particular], because they get the other extreme – they are out in the community with elderly people who are really bunged up

(Interview: nurse 4, personalised intervention, authors' emphasis, pp. 2–3)

management of chronic constipation did not 'come into [her] *role*'. Nevertheless she added that 'healthy eating advice' was part of a wider package of work including 'well-woman' and 'well-man' checks. Therefore, although the topic of chronic constipation was not considered a central area of work for practice nurses, they viewed the provision of diet and lifestyle information as part of their core skill set.

Regarding the second account in *Box 5*, an additional point is Nurse 4's use of the term 'dietary *advice*'. One concern among the trial team was that nurses in the personalised (BCC) arm of the trial would conflate directive advice giving with the counselling approach. However, while nurse 4 – who attended the BCC training – used the term 'advice' in her account, most of the nurses in the personalised arm described the techniques as being familiar, distinct from paternalistic approaches, and in routine use through their smoking cessation and obesity work.

Nurse 4 finished her response by emphasising that *district* nurses see '… the other extreme' of chronic constipation with '… people who are really bunged up'. In this regard, Nurse 4 made a distinction between the *preventative* work of practice nurses through well-person initiatives, and the work of community nurses whose responsibilities include the 'other extreme' of chronic constipation: amelioration and treatment. In this example the aim of the trial – to train practice nurses to *prevent* rather than treat chronic constipation – is lost in the nurses' explanation of why the trial's topic is a low priority.

It is important to consider that while one interpretation of the nurses' accounts is that they were attempting to pass responsibility for chronic constipation to community nurses, this glosses over a valuable message consistently delivered in the nurses' interviews: that chronic constipation was not a problem that was pertinent to the nurses within their routine interactions with patients. Therefore, the trial team had to work within a set of parameters that were not conducive to the trial's success; namely asking practice nurses to engage with a problem that was largely 'invisible' to them. Moreover, while some practice managers viewed chronic constipation as a financial burden to their practice, they reiterated the nurses' position that it was a condition addressed more directly by a GP (through laxative prescription) or by nurses working in the community. One practice manager provided a 'bird's eye' view of the distribution of work across the practice. An extract from this interview is presented in *Box 6*.

Throughout her account, the practice manager made a series of important points regarding the division of labour within the practice, and the specified skill sets of various groups of nurses. While the age of patient populations was not used by the nurses as a means of demarcating professional boundaries, in the interview the practice manager alluded to a broad sector of work that was conducted between community nurses and '… *our older group*'. Following this perspective, the practice manager suggested that the community nurses '*should be* and *would probably benefit from*' involvement in the research, but ultimately did not 'support' the practice in this instance. From this point onwards in the extract, the practice manager sets out the context for the 'failure' of the interventions in her practice. Specifically, the practice nurses were described as an inappropriate substitute to the community nursing team. In this regard the practice managers' response is to assign responsibility for the problem of chronic constipation to health-care professionals beyond the control of the practice. As described earlier, the redirection of responsibility for particular patient populations from one professional group to another has been documented elsewhere in the NHS.[221] In the current account, the practice manager described the practice nurses as having responsibility for defining their own skill sets

BOX 6 *Constipation as a problem 'outside the practice'*

Interviewer: … I think we were talking about why this particular project could be tricky, you mentioned that it's –

Practice manager D: Right okay I think number one was the fact that this particular research project involves *older people* by default you tend you, it tends to be from the nursing side it tends to be *our community nurses* who are involved with *our older group*, erm, and they are the people who *should be* and *would probably benefit from* looking at a research project like this, unfortunately … we were unable to engage them to support us … So [it had to be] *our practice nurses* involved, and they felt that it really wasn't erm their erm *remit*, you know chronic constipation and advice does very much tend to be *outside the practice* erm unfortunately it hasn't worked!

(Interview, practice manager D, authors' emphasis, p. 1)

and spheres of activity. Specifically she explained that '…*they* felt that it really wasn't erm [within their] *remit*'. Consequently, the extract suggests political tensions *within* the practice regarding the distribution of work implicated by LIFELAX. An investigation of the everyday running of practices enrolled into the RCT was beyond the scope of the process evaluation. However, task designation issues within each practice are likely to have contributed to how the trial was perceived in each site, particularly as the trial's topic was comparatively 'unglamorous', involved a population of patients not prioritised in the QOF, and – like all research – included additional work for the clinical staff involved. In some instances practice nurses explained that there had been some direction by senior practice staff – 'a little bit of pressure' (Nurse 9, 16 April 2007) – to cooperate with the trial team, and consequently these nurses may have felt little ownership in the research. This situation arose in part due to the manner in which the trial team contacted and enrolled practices to the trial. Practice enrolment occurred via negotiations between the research team and GPs and practice managers, although most of the research tasks were targeted at nurses. Unfortunately, it was not possible to monitor the degree of consultation that occurred in each practice between senior and nursing staff.

A pertinent issue raised by primary health-care staff enrolled in the trial was the unsuitability of the interventions for practice nurses, and correspondingly their appropriateness for community nurses. However, while community nurses were initially included in the trial protocol, they were quickly identified as a potential confounding factor in the trial design. *Box 7* includes an extract from an audio-recorded subgroup meeting in which the trial team explore reasons for excluding community nurses.

Several interesting methodological points are raised through the extract in *Box 7*. The first is an observation that community nurses are employed by the PCT rather than the practice. This point links to the comments of the practice manager in *Box 6*, namely that the practice did not have absolute authority over the work of the community nurses, and therefore were unable to secure their cooperation in delivering the trial. Nevertheless, as described earlier, the practice manager capitalised on these differences to excuse practice staff from the tasks asked of them by the trial team. The practice manager suggested that in the context of chronic constipation, the research work was more appropriately suited to 'outsiders' in the community; in this example, PCT employed nurses. The second point is that the RCT design – specifically the rationale and practice of randomisation – precluded, or at least rendered very difficult, delivery of training to the most 'appropriate' group of staff: community nurses. As the senior dietitians explains 'The problem is that [community nurses] go from practice to practice so you will end up training a community nurse with the behaviour change [approach] who then goes into your standardised practice [and contaminates the trial]'. In this regard, the methodological limitations of even a cluster RCT design undermined some aspects of the interventions' assessment. Although in principle

BOX 7 *Excluding community nurses from the RCT*

Dietitian: I don't er, I just think it's very hard to get hold of community nurses, they're not employed by the practice, they're employed by the PCT

Trial manager: PCT

Senior dietitian: Can I just put another little fly into that ointment?

Health psychologist: The randomisation

Senior dietitian: The problem is that they do go from practice to practice so you will end up training a community nurse with the behaviour change who then goes into your standardised practice

Health psychologist: That's right, yes

Trial manager: Right

Dietitian 2: Who says 'you should be doing this'?

Senior dietitian: Yes. And they also if they find something that they like, they are really very good at photocopying, and I have experience of this, and they distribute it to every practice that they go to, give it to nurses and say 'do you like this?'. Em in [another study] we trained community nurses if the practices wanted them to be involved and we had our leaflets popping up in our control practices

(Subgroup meeting transcript, 16 March 2004, pp. 23–24)

it would have been possible to use the community nurse as the unit of randomisation in this trial design, this would have required the trial team to identify the case load for each nurse, and to then recruit these patients to the trial. It is unlikely that this approach would have been feasible given the trial team's limitations on access to patient data. Finally, the third related point is that the trial design, despite embracing a pragmatic agenda, conflicted with 'real world' practices regarding the dispersion of skills and materials. At the end of the extract the senior dietitian recounts an episode of normalisation-in-process, when she states 'if [community nurses] find something that they like … they distribute it to every practice that they go to'. Ironically, the RCT disrupted the potential for normalisation by prohibiting the transfer of those techniques and materials that nurses found practically useful in their daily work. These limitations were unavoidable given the brief for a RCT.

Nurses in the personalised arm were sceptical that the training sessions they attended would furnish them with new skills, or improve their practice with patients. The BCC techniques were identified by the nurses as overlapping considerably with their current skill sets. Framing this feedback through the terminology of the NPM, the trial's personalised intervention failed to *dispose* of clinical problems relevant for practice nurses, and did not enhance their *confidence* in working with chronically constipated patients. Neither the 'problem' of chronic constipation, nor the suggested 'solution' via BCC, were reported as valuable or significant for the nurses in their daily work. Given this context, the materials associated with the interventions (leaflets, BCC manual) were praised in their capacity to facilitate a sharing of ideas, or *congruence*, about diet and lifestyle issues between nurse and patient. *Box 8* presents a summary of these points through the account of an additional nurse.

Importantly the quote from Nurse 3 demonstrates some perceived value in the behaviour change tools, particularly with regard to improving congruence between the nurse and patient. However, this positive assessment was made alongside Nurse 3 suggesting that the materials were 'the best bit' of participation in the trial. It is therefore not clear if Nurse 3's praise of the materials was due to their practical merit in facilitating consultations or an attempt to find something positive to report to the interviewer. Nevertheless, Nurse 3 commented that she would value the use of the materials 'in the clinic' with patients outside a trial setting; conspicuously using the term '*our* patients'. Based on this particular account, the tools could be considered as a potential means of facilitating the disposal of *some* clinical problems relating to diet and lifestyle generally. However, none of the nurses described an intention of applying the tools post trial with patients suffering from chronic constipation specifically.

In a recent paper, Salmon *et al.*[219] identified factors affecting the relative attractiveness of research participation for practitioners in primary care in contrast with those in secondary care. The authors suggest that although a research portfolio might boost the careers of clinicians working in hospital settings, the same cannot be said for those established in primary care where research involvement may hold little or no incentive.

BOX 8 *Finding value in the intervention materials*

Nurse 3: … [the leaflets could be] ideal because [patients] could look at the pictures and identify 'well yeah I'm having so many of those a day or this amount of veg, this amount of fruit, or I'm not eating any at all', I did find that one really good to use and I thought it would be good eventually if we could maybe have some to use in the clinic *to use with our patients*, or along those lines, because sometimes you speak to people and you ask them 'which veg do you eat', and they class two peas and things like that as veg, and they're not really aware that there is not a lot of fibre, etc., you know and I found that was a *good way of getting [the information] across* to people

And later in the interview:

Interviewer: Do you think the techniques that [the dietitian] was demonstrating, do you think they differ much or at all from your usual practice? I mean … was there anything *in the techniques themselves* that's different about how you interact with patients?

Nurse 3: Well nothing really *apart from those leaflets*, … I think those information leaflets were really good … I think that was the best thing, [the dietitian] had obviously or whoever had thought a lot about what went into them, and making them easy to use [lowering voice] I think that was the best bit

(Nurse 3, personalised arm, authors' emphasis, p. 2 and p. 5)

Through the process evaluation we explored how practice-based staff viewed involvement in the LIFELAX trial specifically. Although we cannot comment on their experiences in other research settings, the feedback of our respondents suggests that they generally held little interest in the interventions or overall success of the research. Three out of the eight practice-based nurses countered this position by expressing interest in the RCT's topic and success. However, two of the trio were employed as research nurses and the third held aspirations for a career as a nurse practitioner: a goal possibly facilitated by research involvement.

The topic of the trial – and, to some extent, the nature of the interventions – had been preset in the commissioning brief for the research. Consequently, the trial team attempted to meet the brief while also working to meet the realities and demands of clinical practice. With regard to the practice nurses, the trial team experienced frustration as their aspirations for the training packages were not realised. Likewise the nurses struggled to make sense of trial work within the context of their working practice. In attending the training sessions and applying relevant skills with participating patients, the practice nurses were frequently left perplexed by their participation. An analysis of their accounts suggest that they understood the trial as a request to tackle an already successfully managed 'problem' with an untested and time consuming 'solution'. The nurses were therefore *unconvinced* that their time was being used appropriately, and for a worthwhile exercise. These findings lead us to reflect on the importance of programmes of work that use research methods in a timely and appropriate manner. In the case of the LIFELAX trial, an accumulation of evidence regarding the clinical effectiveness of BCC for chronic constipation, prior to a pragmatic trial of nurse training packages, *may* have been valuable. In particular, such evidence may have added weight to the argument that changing current patterns of work within primary care was worthwhile. More importantly, a feasibility study that identified problems with recruitment, low clinical interest, and RM&G issues may have precluded investment in LIFELAX. At the time of funding the HTA did not commission pilot or feasibility studies, although currently the HTA's position on this issue has changed.

A summary of the findings from the practice nurses is presented in *Table 25*. In the third and final section of this chapter, we explore the views of the participating patients.

Making sense of participation in the context of chronic illness

Some of the barriers to the success of the LIFELAX trial, as explained earlier in the chapter, were due to a range of issues concerning RM&G guidelines and MREC rulings, and a notable lack of interest in the research across primary care sites. However, the participants' accounts of their experience also offer a useful perspective

TABLE 25 *Barriers and facilitators to the normalisation of LIFELAX nurse training packages in primary care*

Summary
The nurses reported that the topic of the trial was ill matched to the current work of practice nurses and the way in which chronic constipation was currently managed in primary care. Although the trial assessed the value of changing current practice from *treatment* of the condition to nurse-led *preventative* measures, the nurses generally focused on current patterns of work. Nevertheless some nurses argued that chronic constipation was a comparatively low-priority complaint, that it was successfully treated via laxatives in most cases, and that they were sceptical that motivation was instrumental in patients' experiences of chronic constipation
Additional points
The BCC techniques were identified by some nurses as overlapping with their current skill sets and therefore were not described as providing the nurses with new skills or tools
The materials associated with the interventions (primarily pamphlets) may facilitate a sharing of ideas (*congruence)* about diet and lifestyle issues between nurse and patient, although praise of these materials was made in the context of a comparatively negative description of trial involvement
Some of the nurses questioned the *validity* of attempting to motivate patients whose constipation was caused by lifestyle factors beyond their control. Consequently, rather than enhancing confidence in the conduct of their work, some nurses described the BCC approach as potentially undermining the interaction they had with patients
Due the implementation of randomisation, the community nursing teams who may have found the techniques most applicable were excluded from the trial

regarding how the trial was deployed, and the significance of the interventions for patients suffering chronic constipation. The meaning of the trial for participants was shaped by their individual 'illness trajectories' or, specifically, the manner in which participation met ongoing, idiosyncratic priorities regarding their illness.[222] Specifically, although some participants had reached personally satisfying treatment decisions prior to the trial, others were actively seeking *new solutions* to the management of their chronic constipation. Participants in the two 'active' diet and lifestyle arms of the trial experienced an interaction with one of the practice nurses. Consequently, in these arms, the participants' perception of the research was shaped by how the nurses conveyed – deliberately or subconsciously – their own views of the trial. It was difficult therefore to discern through a single interview with a given participant, sometimes a considerable time after the consultation with the nurse, how these factors independently affected the participants' experiences. Nevertheless, three key topics were central to all accounts. These were: (1) reported motivations for participation; (2) experience of interacting with a nurse in the research consultation (in applicable arms); and (3) understanding of the outcomes of participation in the RCT.

Participation in the LIFELAX trial

The participants' explanations regarding motivation for involvement in LIFELAX centred on the manner in which the trial met their priorities and expectations with regard to their illness. Participants who described having successfully established a means of coping with chronic constipation reported that the trial was a means of benefiting others. However, participants who were seeking solutions to their experience of symptoms identified the trial as an opportunity for adjunct therapy. In some interviews participants moved between these conceptualisations. Data for the process evaluation was collected from each participant through a single interview. Consequently, the motivations expressed by any one individual for participation may have changed over the course of their involvement with the trial. *Box 9* presents the accounts of two participants when asked to describe what they hoped to achieve by participating in the trial.

BOX 9 *Retrospective accounts of motivation for participation in the RCT*

Interviewer: … did you have any particular motivation in being part of this trial, other than you said you had experience of [being in other studies]?

Participant: I was suffering from a combination of [complaints] … we went through a variety of treatment options and we settled I think on [a medication] which seemed to do the trick … only just now unfortunately I'm having [side effects] … Er, in addition to having the [the side effects] I found that I've been [suffering constipation again], even though I was taking the [medication] …

Interviewer: … so do you think in terms of your motivation for being part of this trial, would you say then that you were looking for a solution? Do you think, would that be a fair summary, that you were –

Participant: (interjecting) – Yes, I have been looking for a solution for a long, long time

(Interview, participant ID 1315001, personalised consultation, pp. 1–2)

And:

Interviewer: I think to start with if we could just talk a little bit about how you first came to be involved in the trial, that would be really good

Participant: Right. Um, well first of all I think I had a letter from the [trial team] asking if I would like to take part … Now I didn't think that I *suffered from constipation* at all so I was very surprised when I got this letter and I rang the [trial team] up and said 'Well look I don't suffer from constipation'. I do have [a related illness] so I think perhaps the doctor put my name forward because I'm on [a relevant medication] all the time … I think that's why I was involved in it, but I've never had any history of constipation. But the people said well that was OK they would go ahead with it

Later in the interview:

Interviewer: Do you mind if I ask you if you had any particular motivations for taking part?

Participant: Er no, except, well, no I mean it was sort of they asked me, would I? And I said yes I would. It was just as simple as that really, *I'd no objection to it* … No, no, um as I say I was quite willing to take part in this, *in the survey*. Um and quite willing to leave it at that

(Interview, participant ID 1018009, standardised consultation, authors' emphasis, pp. 1–3)

In the first extract the participant expressed his motivations as trying to find a satisfactory 'solution' to the problem of chronic constipation. Notably, he described a prolonged period of dissatisfaction with his current medication prior to the LIFELAX trial: 'I have been looking for a solution for a long, long time' (ID 1315001). In this respect the participant may be described as orientating towards the trial – at this particular instant – as a 'patient seeking treatment'.[223,224] Conversely, the second participant describes themselves as '[not] suffer[ing] from constipation at all' (ID 1018009), a theme also identified in the STOOL trial.[19] Throughout the extract the second participant explains their surprise at being asked to contribute to the LIFELAX trial, and offers an explanation as to why they might have been identified: 'I think perhaps the doctor put my name forward because I'm on [a relevant medication] all the time' (ID 1018009). In this regard, while the participant understood that they were taking laxative medication, the perceived effectiveness of the treatment was such that constipation (and the taking of laxatives) were not regarded as a problematic feature of daily life.

This perception (of laxatives being an effective solution to constipation) was so entrenched in the accounts of some respondents, that the purpose of the trial was put into question. Therefore, for this individual participation was a result of *meeting a request* from the trial team; '… I mean it was sort of they asked me, would I? And I said yes I would. It was just as simple as that really, *I'd no objection to it'* (ID 1018009). The second respondent is an example of those participants who identified themselves primarily as '*research subjects*' in an RCT, in much the same manner as participants described in a previous paper.[223] For these participants the trial was largely an altruistic exercise that might, potentially, benefit other patients in the future. These conceptualisations were helpful tools in understanding the trial's significance for various participants. Those who were seeking treatment as patients may have benefited most from the personalised BCC consultation as they were by definition actively seeking intervention. However, we found that regardless of randomisation status or orientation to the trial as 'patient' or 'research subject', most participants struggled to make sense of their involvement in the LIFELAX trial. This finding does not reflect on the quality of the LIFELAX participant information materials, but is a common finding in qualitative research exploring the understandings of participants in RCTs.[225]

In recent years researchers have focused on the importance of making sure participants *understand* RCT concepts, rather than simply being able to recall them by rote; however, to date there is no clear method of facilitating this process.[226,227] The practice nurses involved in the trial described the intervention techniques as 'familiar', and therefore the participants may have also struggled to understand the experimental components in the trial design. This is a point discussed in detail below.

The second topic central to the participants' accounts was their understanding of the role of the practice nurse in the trial. The nurses were described both in regard to their perceived *role* and their *performance*. Participants tended to talk about these topics as they articulated what they perceived as poor or unexpected behaviour on the part of the practice nurse. *Box 10* presents two accounts by participants disappointed by the perceived behaviour of the practice nurses.

In the first interview presented in *Box 10*, the participant offered an evocative description of meeting with a practice nurse in the setting of a LIFELAX consultation. The nurse is described as having an attitude quite opposed to the trial, which the participant used in her account to contrast with her own position as a citizen 'happy' to 'benefit … others' (ID 1101003). Throughout the account the participant used a number of explanations for why the nurse may not have been enthused by the study such as having 'an awful lot to do' (ID 1101003) and 'dealing with patients who are ill and who need attention' (ID 1101003). Nevertheless, the participant was disappointed that the nurse '[gave] the impression that she thought it was all going to be a waste of time' (ID 1101003). Finally, the participant contrasted this description of clinical activity with the work of the trial – 'filling in forms' (ID 1101003). In this instance the participant appeared to be disappointed and frustrated by the nurse's attitude, although she demonstrated that she could understand some of the contextual reasons why the nurse might respond in this manner to the extra work involved. Both the nurses and participants shared similarities regarding their participation experience. Both struggled at times to make sense of their participation, and both were required to complete additional work. Consequently, we may interpret the participant's account of the nurses' behaviour as a means of expressing her own frustrations to the researcher. For this participant the trial was an exasperating experience, and the

BOX 10 *Participant accounts of practice nurses in the RCT*

Participant: … when I went to the practice nurse [for the trial consultation] … I think the attitude was, 'eeh, oh yeah' (rolling eyes) you know, 'something else that we've got to do'. Er, well my own attitude was, em, if it's going to be of benefit to others then I'm quite happy to go along with it

Later in the interview:

Participant: … it was at that time, that I gained the impression … oh this terrible, but I did gain the impression that she thought it was all going to be a waste of time. Right, now that is probably because they have an awful lot to do, and their time is, as you have just mentioned, a few minutes ago, it's spent, dealing with patients who are ill and who need attention. Er, not filling in forms. You know what I mean?

(Interview, participant ID 1101003, standardised consultation, p. 3 and p. 6)

Another participant shared her perceptions:

Interviewer: … I know that we've already covered this slightly before, but when you went to see the nurse for this particular trial and she went through the information leaflets, did you get a sense that was different from the conversations that you'd had before, that there was a bit more time there to go through some of that information, or did you not really get that sense?

Participant: Well I got the sense really that 'oh I've been asked to do this as a job, I'm handing out information' erm, but it's, it's information; … you'll *already know it*, but if you read it and it's *just common sense*, you know – which okay things are common sense, – but when you're troubled with constipation it's, you know you would like other little bits of erm, any kind of snippets you can get really

(Interview, participant ID 1018001, standardised consultation, p. 7]

nursing staff served as 'visible' representatives of the trial, essentially the subjects of blame for an unsatisfactory participation experience. Some of these themes reoccur in the second participants' account. However, here, the participant explained why receiving 'common sense' (ID1018001) advice was helpful when suffering from a condition such as chronic constipation. In this instance the nurse's role was identified as being more than a neutral provider of information, but as a person interested in the participant's complaint. The nurse therefore provides information that '… you'll already know' (ID 1018001), but the act of discussing the topic, face-to-face with another individual, was potentially helpful. Unfortunately, the participant's perception was that the nurse was uninterested in the consultation and the trial as a whole.

It should be noted that the inner mechanisms of the trial – and therefore the work of the trial team – were almost entirely hidden from the participants. Consequently, within the participant interviews the most 'visible' components of the trial were the interactions with nurses and the diary exercises. The nurses were therefore *expected* to perform RCT work, and in this regard, the participants did not consider the nurses as independent agents with their own agenda and concerns. Consequently, the work of the practice nurses' was commented upon in a manner that tended to draw criticism as and when problems arose.

The third topic central to the participants' accounts was their attempts to make sense of the outcomes of participation. Regardless of their explanation for involvement or the randomised status of their practice, most participants' accounts were marked by disappointment with respect to their experience in the trial. The participants described having difficulty understanding the manner in which the RCT might produce beneficial outcomes for themselves or others. This difficulty stemmed from the perceived ineffectiveness – or invisibility – of the trials' interventions. For example, it was not clear to either the nurses or the participants how a BCC consultation might differ from a routine interaction – other than in topic and length of time available. Nevertheless, in some instances the participants attempted to positively frame the meaning of participation by emphasising the realised or expected benefits, even if the mechanisms by which these benefits might occur were not fully understood or articulated. One participant, who did not find remediation for her symptoms, expressed hope that others might benefit in some way from her participation (*Box 11*). The account, however, is marked by an overt desire for a personal solution.

In this example the participant was clear that after taking part in the personalised arm of the trial, they did not expect to be able to 'change [their condition] … at the minute' (ID 0815005). For this

BOX 11 *Coping with disappointment: hope in benefit for others*

> *Participant*: I wait for something to happen, I am eating [a recommended diet] and what have you but it hasn't changed anything
>
> Later in the interview:
>
> *Participant*: I would think that there [are] not many different avenues that you could go down with [the personalised consultation], it's either different treatments, I don't think you will change my [condition] with that at the minute er, no I think I will just go along … just follow the lead and hopefully in the end will get a little bit of feedback I'm quite happy with a little bit of feedback on what's going on
>
> *Interviewer*: Well I think that's quite important isn't it for people who are involved to get some –
>
> *Participant*: (interjecting) Oh yes, I just want to know sort of, if you have helped somebody if you have helped somebody then it gives me hope for some reason
>
> (Participant ID 0815005, personalised consultation, authors' emphasis, p. 2 and p. 4)

participant, 'the value' of participation hinged on having 'helped somebody' (ID 0815005) at some other point in time. Consequently, they asked for feedback from the trial team in order that they themselves might have some 'hope' (ID 0815005).

For most participants' involvement in the trial consisted primarily of the daily diary exercise. Participants in both 'active' arms of the trial received information leaflets and advice or BCC that was reported as being unremarkable. Indeed, many participants struggled to recall having 'an intervention' at all. *Box 12* presents an extract from two interviews in which participants explained their interpretation of the trial design, and for one participant, their hope for 'an intervention' at some point in the future.

In the first quote presented in *Box 12*, a participant in the control arm of the trial explained that the diary exercise was a precursor to an intervention: '… what you have to do before anything sort of concrete came out of it' (ID 0223004). Specifically, the diary exercise was seen as a means of assessing 'what's happening' (ID 0223004) for the participants before an intervention could be developed and implemented. Arguably, we might expect an explanation of this type from participants in the control arm of the trial, where an absence of any novel intervention by the trial team was an intentional design feature. However, in the second quote, a participant randomised to the personalised arm of the trial explained how their contribution primarily consisted of '… remembering to fill the book in every day' (ID 0815005). In an attempt to attach some meaning to their experience in the trial, the participant explained that his participation had been valuable if it 'help[ed] anybody else' (ID 0815005); however, he was left seeking a solution to a 'wind problem' (ID 0815005) that had been troubling him long before his participation in the trial. In this respect the trials' interventions were reported by most of the interviewed participants as having little potency with regard to helping them with their health problems. Interestingly, for both the nurses and the participants, the BCC interventions were not regarded as offering anything 'new'. In the case of the participants it is not possible to ascertain if this finding was due to the way in which the nurses deployed the BCC, the inherent qualities of the interventions themselves or a combination of factors. A summary of the findings from interviews with participants is presented in *Table 26*.

Discussion

The assessment of complex interventions can be a challenging process.[228] In the process evaluation, we observed two 'complex interventions': (1) diet and lifestyle training for practice nurses, but, more specifically, (2) the practical conduct of an HTA RCT. In light of the trial's premature closure, data from the qualitative evaluation help to explain some of the processes that led to the trial's closure, and how they might be avoided in future RCTs. Although we can comment on the structure and implementation of LIFELAX (and offer recommendations for future implementation of HTA research), the relative importance of clinical topics such as 'chronic constipation' and the merit of 'BCC' per se are less clear. Specifically through the process evaluation we observed the confluence of several 'trajectories' or processes:

- The implementation of a pragmatic RCT in an 'unsettled environment' of research governance interpretation and ethical judgements.

BOX 12 *Attempting to make sense of participation in the face of disappointment*

Interviewer: … apart from obviously getting the diaries that you didn't expect, has other aspects of [the trial] been what you thought it would be or has it been different?

Participant: Erm I thought initially *this was what you would have to do before anything sort of concrete came out of it*, … obviously you have got to take *a wide survey* of exactly what's happening and then you obviously take it from there *so expect something different after they have all sort of consulted all the diaries* belonging to everyone that's participated in the trial *and then* I think something might be gained from it

(Interview, participant ID 0223004, control arm, authors' emphasis, pp. 2–3)

And:

Participant: … no [the trial] hasn't been a hassle like I mean er, *its just remembering to fill the book in every day* like ya know just at the end of the week … I just put no no no all the way down and when I was bad I just wrote in that I was bad and when I was on holiday I just put in the book there that I was on holiday and had a bout of diarrhoea and what I took to stop it and er *but I have never had any hassle or anything out of it no*

Interviewer: Right well thank you very much

Participant: It has been worth er you know *if it can help anybody else well that's fair enough* like so just that *I would like to get rid of this problem* what I have got this wind problem and I cannot at the moment its gone on for a long time

(Interview, participant ID 1105001, standardised consultation, authors' emphasis, pp. 6–7)

TABLE 26 *Factors affecting the experience of the LIFELAX trial for participants*

Some participants reported a lack of understanding (*congruence)* between themselves and the practice nurse regarding the value of the research. For some participants, their encounter with the practice nurse was a demoralising experience. In particular, while some participants viewed their chronic constipation as an important problem they reported that the nurse did not appear to see the research as worthwhile
For most of the participants seeking medical interventions, the BCC or standardised advice consultations failed to help them find solutions to problems related to health, diet or lifestyle issues. In contrast, three participants explicitly reported some benefits (either psychological and/or physiological) from a behaviour change consultation and described making a number of lifestyle changes as a result
It is not possible, due to the pragmatic design of the trial, to separate the effects of BCC from its delivery by nurses
The participants made sense of their participation largely through the daily diary exercise. Due to this exercise, some participants interpreted the trial as 'survey' research

- The response of practice staff to involvement in an RCT concerning a condition not prioritised in GMS contracts.
- The response of practice nurses to proposed changes in their work patterns.
- The responses of practice staff to the problematisation of chronic constipation: practice nurses perceived chronic constipation to be a condition already successfully managed by laxatives.
- The response of the nurses to BCC training as delivered by dietitians or nutritionists.
- The response of participants to involvement in a pragmatic RCT (including management of expectations and research-related tasks, such as the daily diary).
- The response of participants in the diet and lifestyle arms to the combined stimuli of the LIFELAX trial and an interaction with a practice nurse.

In this report we have attempted to describe the interaction of these processes on the success of the LIFELAX trial. Nevertheless, RM&G and ethics issues aside, it is not possible to isolate the factors from one another. For example, had the training been delivered to community nurses the response of these staff *may* have differed from that of the practice nurses in LIFELAX.

As the embedded process evaluation study was ethnographic, qualitative research techniques were employed, and it was therefore not appropriate to set out our research questions in hypothetical form. However, at the outset, we attempted to address the following specific questions:

1. *Formation* How are ideas about the appropriateness of health technologies and their clinical applications formed and mobilised in practice; how are the interests

of consumers and other users defined and incorporated in the organisation of the trial?

The process evaluation explains some of the reasons for the early closure of LIFELAX and we draw a number of conclusions about the structural processes of HTA assessment from these data. However, it is not possible to make claims about specific public health topics, such as the significance of chronic constipation for primary care medicine. We did observe that practice nurses and managers perceive chronic constipation to be successfully managed by laxatives, and that roughly one-half our sample of participants also considered themselves either not to suffer from constipation or that they successfully managed their symptoms through the routine use of laxatives. However, the nurses also explained that they did not work with patients presenting primarily for chronic constipation. The 'problem' of chronic constipation may largely be one of economics for senior practice staff, or an issue of concern for community nurses, or an issue for some, but certainly not all, patients.

If we consider the 'lessons learnt' for future HTA trials, it is important to understand how and why the LIFELAX trial was commissioned considering the response of practices. A systematic review underpinning the commissioning of LIFELAX, identified both chronic constipation and diet/lifestyle interventions as pertinent topics in primary care. This finding, taken on face value, appears to be at odds with the outcome of the process evaluation. However, the cost of laxatives and the dependence of patients on medication were issues that concerned some practice staff in interviews. Nevertheless, the relative priority of this problem when compared with others in the practice was not high.

Most of the trial team's efforts were invested in ensuring that the RCT was successfully embedded in individual practices and across PCT sites. However, the response of practice staff to the trial's topic and interventions were identified only after the RCT had been deployed. These issues may have been identified through a prior feasibility study, if one had been funded. A small pilot study was conducted during the development of training materials. However, this work was focused on the development of BCC materials and not on the feasibility of a larger trial.

2. *Integration* How are specific clinical and methodological problems within an RCT identified and resolved within professional groups and networks; how is the trial integrated into the existing organisation of clinical service provision, and what professional and organisational dynamics are involved in this integration; how is participation in the RCT negotiated and understood by subjects?

This is a multifaceted question and, as such, we have addressed it in the current chapter via several different means. With regard to the clinical and methodological problems of the LIFELAX trial, the trial team engaged in a considerable amount of negotiation and bureaucratic work in order to integrate the trial in clinical environments, and to meet RM&G and MREC requests. We have discussed this process through the NPM constructs of *interactional workability* and *contextual integration*. Notably, we found that the RCT relied heavily on cooperative networks. Cooperation and a shared understanding of goals (*congruence)* were achieved through the social skills of the trial manager and his ability to negotiate access to resources with relevant personnel across NHS organisations at both a national, and local (PCT) level. This observation highlights the necessary (though potentially underacknowledged) skills required of trial managers in the current climate of primary care research.

Due to the decision of the MREC regarding SSAs and access to patient data, the evolving nature of RM&G guidelines, and various interpretations of these guidelines across PCT sites, the trial team were under pressure to continually develop creative and workable solutions to emerging problems. This formed a barrier to the satisfactory and timely achievement (*disposal*) of essential milestones – such as recruitment – in the delivery of the trial. A review of the *practical implementation* of MREC decisions and RM&G guidelines in primary care is also necessary in order to identify how to promote quality research while meeting ethical standards.

We addressed the research question 'how is participation in the RCT negotiated and understood by subjects?' through the NPM constructs of *interactional workability* and *relational integration*. Specifically, we found that some participants reported a lack of understanding or *congruence* between themselves and the practice nurse regarding the value of the research. For some participants, their encounter with the practice nurse was a demoralising experience as the nurse appeared to view the trial's interventions as a poor use of time. Moreover, for most of the

participants who sought medical interventions, the BCC or standardised advice consultations failed to help them *dispose* of problems related to health, diet or lifestyle issues. When describing their experiences in the RCT, the participants reported that the daily diary exercise was the most salient part. Most of the participants therefore struggled to make sense of the mechanics of the trial and how such a diary might usefully contribute to the amelioration of their, or others, chronic constipation. Therefore, whether participants viewed their constipation as problematic or not, both groups reported that they struggled to see how the trial would lead to results that would benefit suffers of chronic constipation. This finding may result from the intrinsically confusing experience of trial participation as reported in the literature,[229–231] an issue more specific to the LIFELAX trial, such as the practice nurses' perceptions of the research and their subsequent behaviour with participants, or a combination of factors.

3. *Implementation* How are the production of results negotiated and organised within networks of researchers; how are its results mediated to the wider community and how is this negotiated and organised, both formally (through report writing and presentation), and informally how are the mechanisms and results of the trial understood by subjects?

Following the premature closure of the LIFELAX RCT it was not possible to collect data relating to the development and publication of outputs from the trial. However, we have discussed the manner in which the participants attempted to understand the mechanisms and results of the trial through the context of their own illness trajectories and the NPM constructs *of interactional workability* and *relational integration*.

4. *What lessons can be learned that will improve the organisation and conduct of HTA RCTs in the UK – and further afield?* The study holds important implications for the organisation and conduct of HTA. It is important that its results can inform and develop both policy and practice?

A number of issues regarding the development and implementation of RCTs have been identified through the conduct of the process evaluation. The problem of the trial's topic, setting and training packages may have been identified had a prior feasibility study been conducted. At the time of the LIFELAX trial the HTA did not fund pilot studies of this nature, although the HTA have now changed their policy in this regard. However numerous system wide problems – such as the changing RM&G guidelines and research briefs that did not match GMS contracts – also taxed the capacity of the trial to be successful. Following the results of the process evaluation, and the input of several of the reviewers of this report, we suggest the following:

- Improved means and methods of communication are required between governance bodies, MRECs and researchers regarding the best way to conduct RCTs that are ethically, methodologically, and practically sound.
- There is a need for a clear and consistent means of applying for RM&G approval across PCTs.
- There is a clear need for pilot studies prior to the design and implementation of HTA RCTs. The pilot study should:
  - Assess the feasibility of all aspects of the intended research but specifically ensure that the assumptions underpinning the study are correct. These assumptions may be multiple but should ensure that: (1) there is an identified need for a technological intervention; (2) the intended beneficiaries also perceive a need for intervention and are in equipoise regarding the proposed interventions and control; and (3) the definition of the need or problem is commensurate between researchers, users and beneficiaries.
  - Pilot studies should assess whether the interventions will enable the intended users and/or beneficiaries to achieve relevant goals (such as *disposal* of symptoms).
  - Pilot studies should assess whether the intended interventions fit within existing patterns of work, and where they do not, assess the likely disruption and acceptability to intended users.
  - Pilot studies designed to assess the feasibility of the research should be conducted prior to any significant investment in the development of an RCT.

Conclusions

Through application of the NPM we were able to identify a number of factors that contributed to the premature closure of the LIFELAX

RCT. Evaluation of the trial raises a number of important considerations for the deployment of other trials of complex interventions in primary care. In particular, the administrative difficulties encountered by the LIFELAX trial team, regarding the application of RM&G guidelines and research ethics, were indicative of the unsettled climate at the time of the trial, also experienced and reported by other researchers.[19,215] Nevertheless, research should be conducted to explore how the processes of implementing RCTs in primary care can be practically facilitated, and how procedures may be standardised and streamlined. In addition, it is important for funders such as the HTA to commission studies using appropriate forms of assessment. RCTs may not always be the most suitable method, particularly in the initial stages of development for new and complex technologies.

The trial team developed innovative solutions to practical problems of implementation. This work illustrated the importance of social, as well as technical, competence in the delivery of a multicentred RCT. However, there is a significant gap in the literature exploring how RCTs are practically accomplished. While the process evaluation contributed towards addressing this shortfall, further research is needed to explore the practical conduct of RCTs in different contexts in order to better understand the processes underpinning the formation of medical evidence.

Conventionally, when a large project fails, stakeholders attempt to identify the causal factors for this outcome. However, in the LIFELAX RCT, there was no central agent of blame for the trial's failure. A number of significant problems accumulated across the life of the research to prevent the RCT from moving forwards. These structural problems included the contemporaneous climate of uncertainty regarding interpretation of ethical and RM&G governance, changing priorities in primary care expressed though the GMS contract, and a general lack of enthusiasm or commitment for research in primary care. Specifically, the clinical environment in which the LIFELAX trial was situated was largely indifferent to the research. Although the trial team worked hard to develop workable solutions to these problems, the numerous and unforeseeable issues encountered by the trial team exhausted the capacity of LIFELAX to be a workable trial.

Chapter 7
Conclusions

Due to the low number of participants in the trial, we are unable to draw any firm conclusions about the effectiveness of the interventions in LIFELAX. Nonetheless, at the conclusion of this study, there are a number of issues that we wish to highlight as they had a major impact upon the conduct and progress of the trial. We believe that they are relevant to anyone else conducting research on a similar topic or in a similar population.

Pilot studies

At the time of commissioning, the HTA did not fund pilot studies. If a rehearsal (external) pilot trial or feasibility study had been conducted first then it is likely that the full LIFELAX trial would either never have been commissioned or if it had, it would have had a major methodological overhaul. We are pleased that pilot and feasibility studies are now part of the HTA commissioning process.

Choice of data collection methods

Our findings suggest that the range of data collection methods we employed in LIFELAX were acceptable for use in a population of this age with constipation. The self-completion questionnaire response rates in excess of 80% suggests that despite the length of the questionnaire, the time taken to complete it and the added burden of the daily diary, at the first two time points at least respondent fatigue was not an issue.

Analyses of the response rates and item response rates suggest that the daily diary was not troublesome to participants. We would propose that a diary of this nature to collect information about bowel function and medication is not burdensome to complete and is a satisfactory way of gathering such information.

Defining 'eligibility' for studies of constipation

The experiences of both the STOOL Trial[19] and LIFELAX would suggest that being able to define 'constipation' in a way that is both measurable and acceptable to all stakeholders is vital to future research in this field. When people do not think that they have a particular condition then it seems unlikely that they would be interested in or motivated to participate in research into that condition.

Though a common complaint of industrialised societies,[9] there is much variability in definition of constipation, both within the medical literature and between patients and medical professionals.[8] Some attempts as at a definition have used the frequency of bowel movements.[20,21] Clinical definitions do exist within the Rome II[22] and III[23] criteria for functional constipation.

In the Rome II criteria for functional constipation,[22] two or more of the following symptoms must have present for at least 12 consecutive weeks in the previous 12 months for a diagnosis of constipation:

- straining in more than one in four defecations
- lumpy or hard stools in more than one in four defecations
- sensation of incomplete evacuation in more than one in four defecations
- manual procedures (e.g. digital evacuation or support of the pelvic floor) in more than one in four defecations; and
- fewer than three defecations per week.

In the Rome III criteria a somewhat less restrictive time frame has been introduced.[23]

Practitioners, however, appear unlikely to apply the above criteria in their clinical practice and constipation is typically a subjective diagnosis.[18] Nonetheless, a level of consensus does exist among clinicians over the wide variation between individuals in the normal frequency of bowel

movements (from three times per day to three times per week being normal).[12] The perceptions of older people reported by a small number of previous studies suggest that lay definitions of constipation differ from professional criteria.[14,16,17] From the STOOL report it is apparent that frequency and 'ease' of bowel movements, however, are key components of constipation for the majority of older people.[19]

Our belief is that while there is such a lack of agreement – both within clinicians and patients, and between the two parties – as to what constipation is then recruiting to studies of 'patients with chronic constipation' will remain difficult. If objective criteria such as Rome II/III, or the number of laxatives prescribed in a given time frame are met with the circular argument from patients of 'I take laxatives which produce my desired frequency of bowel movements, and therefore I am not constipated' it would seem there is a hurdle that is particularly troublesome to overcome.

Difficulty implementing the LIFELAX trial

LIFELAX fulfilled all the criteria of a 'marketable trial'.[232] LIFELAX was designed as a pragmatic[113] three-armed cluster RCT to compare laxative treatment (current practice) 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) in the management of chronic constipation in older people. LIFELAX was to be conducted in north-east England and was to recruit patients aged ≥ 55 years, registered with practices participating in the trial, with a current diagnosis of functional constipation.

Like the STOOL trial, LIFELAX was not successful in recruiting patients to the trial and experienced difficulty in encouraging general practices to fully engage with the research.

Though largely anecdotal and based upon the experiences and beliefs of the wider research team and collaborating GPs since the turn of the century, the climate of research has changed and there are now considerable barriers to complex trials of 'routine' interventions.

Ethics committees reacted (some would say over-reacted) to a number of landmark documents including the report of the Alder Hey enquiry,[198] the European Human Rights Act[199] (and its implementation) and preparation for the enactment of the EU Clinical Trials Directive. As a result, the guidelines to which ethics committees adhered became more prescriptive and committees became more risk aware and averse, and took measures to mitigate risk where possible. The publication of the *Research Governance Framework for Health and Social Care*[200] created further challenges with guidance and decisions taken at a local level often appearing to be contradictory to national advice. Ethics committees and NHS Trusts, faced with the introduction of a more prescriptive and bureaucratic framework, were unable to respond to the increasing workload generated. Our experiences in these respects are echoed by other researchers conducting multicentre research involving primary care at a similar time.[201–203]

In addition to the inevitable delays created by these developments, the necessity for participants to 'opt in' to LIFELAX and the apparent removal of direct contact with the research team until much later in the research process was one of the major issues of concern to both the research team and the TSC. This model has major implications for health services research in the future[204] and by implementing such a model, one immediately decreases the likelihood of participation and increases the risk of participation bias.[205] Communication between a committed trial team and the participant is crucial to the success of a trial. Opportunities for those most familiar with the study design and processes (i.e. the research team) to explain the trial or discuss any aspect of participation diminish once the GP practice becomes the primary contact point for information in the early stages of the trial.

We are pleased that, since LIFELAX, many of the proposed measures to streamline the research process are slowly being implemented. The Integrated Research Application System is now running and continues to be revised. This will simplify the entire ethics and research governance approval process, especially for multicentre studies. The Research Passport (its imminent introduction was heralded during the set-up of LIFELAX), when available, will add to innovations such as the Central Sign-off Process for NHS R&D approval, and will hopefully further reduce the bureaucracy of the research process.

Insight from process evaluation

Through application of the NPM[233] we were able to identify a number of factors that contributed to the premature closure of the LIFELAX RCT. However, it is important to note that within the constraints set by the commissioning brief – including the topic of the trial and nature of the interventions – the trial team could not have produced a successful outcome. Evaluation of this trial raises a number of important considerations for the deployment of other trials of complex interventions in primary care. In particular the bureaucratic difficulties encountered by the LIFELAX trial team, regarding the application of RM&G guidelines and research ethics, were indicative of the unsettled climate at the time of the trial, also experienced and reported by other researchers.[19,215] Nevertheless, research should be conducted to explore how the processes of implementing RCTs in primary care can be practically facilitated, and how procedures may be standardised and streamlined.

The trial team developed innovative solutions to practical problems of implementation. This work illustrated the centrality of socially-mediated processes across the lifespan of the RCT. There is a significant gap in the literature exploring how RCTs are practically accomplished. While the process evaluation contributed towards addressing this shortfall, further research is needed to explore the practical conduct of RCTs in different contexts in order to better understand the processes underpinning the formation of medical evidence.

Conventionally, when a large project fails, stakeholders attempt to identify the causal factors for this outcome. However, in the LIFELAX RCT, there was no central agent of blame for the trial's failure. A number of significant problems accumulated across the life of the research to prevent the RCT from moving forward. These structural problems included the contemporaneous climate of uncertainty regarding 'correct' interpretation of ethical and RM&G governance, changing priorities in primary care expressed though the GMC contract, and a general lack of enthusiasm or commitment for research in primary care. Specifically, the clinical environment in which the LIFELAX trial was situated was largely indifferent to the research. Although the trial team worked hard to develop workable solutions to these problems, the numerous and unforeseeable issues encountered by the trial team exhausted the capacity of LIFELAX to be a workable trial.

Recommendations

The issues raised in this report are many and complex, some are condition and time bound (RM&G framework), and, as such, we are reluctant to make stringent recommendations as there may be little usefulness in doing so. However, there are a number of key learning points that we can highlight in the belief that these can be of use to researchers planning an RCT of a complex intervention in the future.

- Our experience suggests that the topic under investigation needs to be relevant to both the people delivering the intervention and those receiving the intervention.
- Rather than launching straight into conducting a full-scale intervention and trial, work needs to be undertaken to ascertain whether such a trial is feasible (we are pleased that pilot and feasibility studies are now part of the commissioning process for the HTA).
- The inclusion criteria need to be clear and comprehensible to both the people identifying participants and the participants themselves.
- If a 'train-the-trainer' approach is to be used for intervention delivery, there needs to be confidence that the trainees are fully supportive and motivated rather than participating because their institution has agreed to take part.

Although it is unclear whether 'payment' or financial incentives would make a future intervention a success, attention needs to be paid to the current funding arrangements and priority topic areas for the health-care practitioners with whom researchers will be working. Topics within the QOF have a much higher profile, interest and importance.

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(*Members of the trial team who are also authors; **members of the trial team who are applicants, but not authors.)

Contribution of authors and other team members

Contribution to the study

Professor Roger Barton** (Professor of Clinical Medicine, Newcastle University and Director of Research, Northumbria Healthcare Trust) developed the protocol and provided clinical advice to the study. Professor Elaine McColl* (Director, Newcastle Clinical Trials Unit) was the CI. She was responsible for the overall management of the study, developed the protocol and edited the report for publication. Dr Richard Curless** (Consultant Physician) developed the protocol. Professor John Bond* (Professor of Social Gerontology and Health Services Research) developed the protocol, project managed the study and edited the report for publication. Professor Carl May* (Professor of the Sociology of Healthcare) developed the protocol of the Integrated Process Evaluation and edited the report for publication. Mr Chris Speed* (Research Associate) was the trial manager and main researcher on the project. He was responsible for the day-to-day management of the trial and recruitment of practices and patients to the trial. He contributed to the development of the behaviour change interventions. He was also responsible for preparing the report for publication. Mr Ben Heaven* (Junior Research Associate) was responsible for conducting the Integrated Process Evaluation and preparing the report for publication. Professor Greg Rubin* (Professor of General Practice and Clinical Director of NoReN) developed the protocol, provided clinical advice and managed the relationships between the study team and general practice. Professor Ashley Adamson* (Dietitian and Nutritionist), Professor Paula Moynihan* (Dietitian and Nutritionist) and Dr Sally Corbett* (Health Psychologist) contributed to the development of the behaviour change interventions. Dr Amelia Lake* (Dietitian and Public Health Nutritionist) contributed to the development of the behaviour change interventions and was jointly responsible for training practice nurses to deliver the intervention. Mrs Yolande Causebrook (Nutritionist) was jointly responsible for training

practice nurses to deliver the intervention. Ms Anna Brookes (Nutrition Student) assisted with the development of the patient information and intervention materials. Dr Nick Steen* (Principal Research Associate – statistician) developed the protocol and provided statistical advice throughout the trial. Ms Alessandra Vanoli* (Senior Research Associate – health economist) developed the protocol for the economic evaluation. Mr Peter McMeekin* (Research Associate – health economist) conducted the economic analysis for the study.

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Contribution to the report

Mr Chris Speed wrote the final report. Mr Ben Heaven wrote the sections of the final report which related to the integrated process evaluation. Professors Elaine McColl and John Bond edited the report. All members of the project team were responsible for critical review of the report and comments were also received from members of the Trial Steering Committee.

Publications

Lake A. Constipation in the older patient. *Com Nutr* 2004;**4**:23–5.

Lake A, Speed C, Brookes A, Heaven B, Adamson AJ, Moynihan P, *et al.* Development of a series of PILs for constipation using a range of cognitive interview techniques: LIFELAX. *BMC Health Serv Res* 2007;**7**:3.

References

1. Petticrew M, Watt I, Sheldon T. Systematic review of the effectiveness of laxatives in the elderly. *Health Technol Assess* 1997;**1**(13).

2. O'Keefe EA, Talley NJ, Zinsmeister AR, Jacobsen SJ. Bowel disorders impair functional status and quality of life in the elderly: a population-based study. *J Gerontol* 1995;**50A**:M184–9.

3. Glia A, Lindberg G. Quality of life in patients with different types of functional constipation. *Scand J Gastroenterol* 1997;**32**:1083–9.

4. Singh G, Kahler K, Bharathi V, Mithal A, Omar M, Triadafilopoulos G. Adults with chronic constipation have significant health care resource utilization costs of care. *Am J Gastroenterol* 2004;**99**:S227.

5. McCormick A, Fleming DF, Charlton J. *Morbidity statistics from general practice: fourth national study*. OPCS: London;1995.

6. Passmore AP. Economic aspects of pharmacotherapy for chronic constipation. *Pharmacoeconomics* 1995; **7**:14–24.

7. NHS Health and Social Care Information Centre. *Prescription cost analysis: England 2005* (prescription items dispensed in the community in England and listed alphabetically within chemical entity by therapeutic class). Leeds: NHS Health and Social Care Information Centre, Health Care Statistics;2006.

8. Camilleri M, Thompson WG, Fleshman JW, Pemberton JH. Clinical management of intractable constipation. *Ann Int Med* 1994;**121**:520–8.

9. Gilliland R, Heymen S, Altomare DF, Park UC, Vickers D, Wexner SD. Outcome and predictors of success of biofeedback for constipation. *Br J Surg* 1997;**84**:1123–6.

10. Prather CM, Ortiz-Camacho CP. Evaluation and treatment of constipation and fecal impaction in adults. *Mayo Clin Proc* 1998;**73**:881–6.

11. Baden-Powell R. *Scouting for boys*. London: Horace Cox; 1908.

12. Drossman DA, Li Z, Andruzzi E, Temple RD, Talley NJ, Thompson WG, *et al*. US householder survey of functional gastrointestinal disorders: prevalence, sociodemography, health impact. *Dig Dis Sci* 1993;**38**:1569–80.

13. Heaton KW, Radvan J, Cripps H, Mountford RA, Braddon FE, Hughes AO. Defecation frequency and timing, stool form in the general population: a prospective study. *Gut* 1992;**33**:818–24.

14. Probert CS, Emmett PM, Heaton KW. Some determinants of whole-gut transit time: a population-based study. *Q J Med* 1995;**88**:311–15.

15. Heaton KW, Cripps HA. Straining at stool and laxative taking in an English population. *Dig Dis Sci* 1993;**38**:1004–8.

16. MacDonald L, Freeling P. Bowels: beliefs and behaviour. *Fam Pract* 1986;**3**:80–4.

17. Annells M, Koch T. Older people seeking solutions to constipation: the laxative mire. *J Clin Nurs* 2002;**11**:603–12.

18. Moriarty KJ, O'Donoghue N. *Constipation, in ABC of colorectal diseases*. London: BMJ Books; 1999. pp. 8–13.

19. Mihaylov S, Stark C, McColl E, Steen N, Vanoli A, Rubin G, *et al.* Stepped treatment of older adults on laxatives. The STOOL trial. *Health Technol Assess* 2008;**12**(13).

20. Whitehead WE, Drinkwater D, Cheskin LJ, Heller BR, Schuster MM. Constipation in the elderly living at home: definition, prevalence, relationship to lifestyle and health status. *J Am Geriatr Soc* 1989;**37**:423–9.

21. Wolfsen CR, Barker JC, Mitteness LS. Constipation in the daily lives of frail elderly people. *Arch Fam Med* 1993;**2**:853–8.

22. Thompson WG, Longstreth GF, Drossman DA, Heaton KW, Irvine EJ, Müller-Lissner SA. Functional bowel disorders and functional abdominal pain. *Gut* 1999;**45**(Suppl. II):43–7.

23. Douglas AD. The Functional Gastrointestinal Disorders and the Rome III Process. *Gastroenterology* 2006;**130**:1377–90.

24. Higgins PDR, Johanson JF. Epidemiology of constipation in North America: a systematic review. *Am J Gastroenterol* 2004;**99**:750–9.

25. Lea R, Hopkins V, Hastleton J, Houghton LA, Whorwell PJ. Diagnostic criteria for irritable bowel syndrome: utility and applicability in clinical practice. *Digestion* 2004;**70**:210–13.

26. Gladman LM, Gorard DA. General practitioner and hospital specialist attitudes to functional gastrointestinal disorders. *Aliment Pharmacol Ther* 2003;**17**:651–4.

27. Moore-Gillon V. Constipation: what does the patient mean? *J R Soc Med* 1984;**77**:108–10.

28. Nakaji S, Matsuzaka M, Umeda T, Shimoyama T, Sugawara K, Sakamoto J, *et al.* A population-based study on defecatory conditions in Japanese subjects: methods for self-evaluation. *Tohoku J Exp Med* 2004;**203**:97–104.

29. Romero Y, Evans JM, Fleming KC, Phillips SF. Constipation and fecal incontinence in the elderly. *Mayo Clin Proc* 1996;**71**:81–92.

30. Lennard-Jones JE. Clinical management of constipation. *Pharmacology* 199;**47**(Suppl. 1):216–23.

31. Glia A, Lindberg G, Nilsson LH, Mihocsa L, Akerlund JE. Clinical value of symptom assessment in patients with constipation. *Dis Colon Rectum* 1999;**42**:1401–8.

32. Connell AM, Hilton C, Irvine G, Lennard-Jones JE, Misiewicz JJ. Variation of bowel habit in two population samples. *Br Med J* 1965;**i**:1099.

33. Johanson JF, Sonnenberg A, Koch TA. Clinical epidemiology of chronic constipation. *J Clin Gastroenterol* 1989;**11**:525–36.

34. Thompson WG, Heaton KW. Functional bowel disorders in apparently healthy people. *Gastroenterology* 1980;**79**:283–8.

35. Talley NJ, Fleming KC, Evans JM, O'Keefe EA, Weaver AL, Zinsmeister AR, *et al.* Constipation in an elderly community: a study of prevalence and potential risk factors. *Am J Gastroenterol* 1996;**91**:19–25.

36. Talley NJ, Weaver AL, Zinsmeister AR, Melton LJ 3rd. Functional constipation and outlet delay: a population-based study. *Gastroenterology* 1993;**105**:781–90.

37. McCormick A, Fleming D, Charlton J. *Morbidity statistics from general practice: fourth national study*. London: Office of Population Censuses and Surveys; 1995. p. 379.

38. Marquis P, De La Loge C, Dubois D, McDermott A, Chassany O. Development and validation of the patient assessment of constipation quality of life questionnaire. *Scand J Gastroenterol* 2005;**40**:540–51.

39. Irvine EJ, Ferazzi S, Pare P, Thompson WG, Rance L. Health-related quality of life in functional GI disorders: focus on constipation and resource utilization. *Am J Gastroenterol* 2002;**97**:1986–93.

40. Gallagher P, O'Mahony D, Quigley EMM. Management of chronic constipation in the elderly. *Drugs Aging* 2008;**25**:807–21.

41. Petticrew M, Rodgers M, Booth A. Effectiveness of laxatives in adults. *Qual Health Care* 2001;**10**:268–73.

42. Cummings JH. The effect of dietary fiber on faecal weight and composition. In Spiller GA, editor. *CRC handbook of dietary fiber in human nutrition*. Boca Raton, FL: CRC Press; 2001.

43. Burkitt DP, Walker ARP, Painter NS. Effect of dietary fibre on stools and transit times and its role in the causation of disease. *Lancet* 1972;1408–11.

44. Bingham SA, Day NE, Luben R, Ferrari P, Slimani N, Norat T, *et al.* Dietary fibre in food and protection against colorectal cancer in the European Prospective Investigation into Cancer and Nutrition (EPIC): an observational study. *Lancet* 2003;**361**:1496–501.

45. Kamm MA. Constipation and its management. *BMJ* 2003;**327**:459–60.

46. American Gastroenterological Association. American Gastroenterological Association Medical Position Statement: guidelines on constipation. *Gastroenterology* 2000;**119**:1761–78.

47. Castle SC. Constipation: endemic in the elderly? Gerontopathophysiology, evaluation and management. *Geriatr Med* 1989;**73**:1497–509.

48. Doughty DB. When fiber is not enough: current thinking on constipation management. *Ostomy Wound Manage* 2002;**48**:30–41.

49. Chen HL, Haack VS, Janecky CW, Vollendorf NW, Marlett JA. Mechanism by which wheat bran and oat bran increase stool weight in humans. *Am J Clin Nutr* 1998;**68**:711–19.

50. Kay RM. Dietary fiber. *J Lipid Res* 1982;**23**:221–42.

51. Stephen AM, Cummings JH. Mechanism of action of dietary fibre in the human colon. *Nature* 1980;**284**:283–4.

52. Hope AK, Down EC. Dietary fibre and fluid in the control of constipation in a nursing home population. *Med J Aust* 1986;**144**:306–7.

53. Badiali D, Corazziari E, Habib FI, Tomei E, Bausano G, Magrini P, *et al.* Effect of wheat bran in treatment of chronic nonorganic constipation. A double blind controlled trial. *Dig Dis Sci* 1995;**40**:349–56.

54. Gear JS, Brodribb AJ, Ware A, Mann JI. Fibre and bowel transit times. *Br J Nutr* 1981;**45**:77–82.

55. Marlett JA, McBurney MI, Slavin JL. Position of the American Dietetic Association: health implications of dietary fiber. *J Am Diet Assoc* 2002;**102**:993–1000.

56. Gregory J, Foster K, Tyler H, Wiseman M. *The dietary and nutritional survey of British adults*. London: Office of Population Censuses and Surveys; 1990.

57. Finch S, Doyle W, Lowe C, Bates CJ, Prentice A, Smithers G, *et al.* National Diet and Nutrition Survey: people aged 65 years and over. London: The Stationery Office; 1998.

58. Dukas L, Willett WC, Giovannucci EL. Association between physical activity, fiber intake, other lifestyle variables and constipation in a study of women. *Am J Gastroenterol* 2003;**98**:1790–6.

59. Kenny KA, Skelly JM. Dietary fiber for constipation in older adults: a systematic review. *Clin Effect Nurs* 2001; **5**:120–8.

60. Lindeman RD, Romero LJ, Liang HC, Baumgartner RN, Koehler KM, Garry PJ. Do elderly persons need to be encouraged to drink more fluids? *J Gerontol A Biol Sci Med Sci* 2000;**55**:M361–5.

61. Chung BD, Parekh U, Sellin JH. Effect of increased fluid intake on stool output in normal healthy volunteers. *J Clin Gastroenterol* 1999; **28**:29–32.

62. Klauser AG, Beck A, Schindlbeck NE, Müller-Lissner SA. Low fluid intake lowers stool output in healthy male volunteers. *Z Gastroenterol* 1990;**28**:606–9.

63. Rodrigues-Fisher LC, Bourguignon BV. Good, Dietary fiber nursing intervention: prevention of constipation in older adults. *Clin Nurs Res* 1993;**2**:464–77.

64. Marteau P, Boutron-Ruault MC. Nutritional advantages of probiotics and prebiotics. *Br J Nutr* 2002;**87**(Suppl. 2):S153–7.

65. Gibson GR. Dietary modulation of the human gut microflora using the prebiotics oligofructose and inulin. *J Nutr* 1999;**129**:1438.

66. Schrezenmeir J, de Verse M. Probiotics, prebiotics and synbiotics: approaching a definition. *Am J Clin Nutr* 2001;**73**:S361–4.

67. Marteau P, Seksik P, Jian R. Probiotics and intestinal health effects: a clinical perspective. *Br J Nutr* 2002;**88**:S51–7.

68. Meance S, Cayuela C, Turchet P, Raimondi A, Lucas C, Antoine JM. A fermented milk with a *Bifidobacterium* probiotic strain DN-173 010 shortened oro-fecal gut transit time in elderly. *Microb Ecol Health Dis* 2001;**13**:217–22.

69. Pathmakanthan S, Meance S, Edwards CE. Probiotics: a review of human studies to date and methodological approaches. *Micr Ecol Health Dis* 2000;**12**(Suppl. 2):10–30.

70. Cummings JH, Macfarlane GT. Gastrointestinal effects of prebiotics. *Br J Nutr* 2002;**87** (Suppl. 2):145–51.

71. Moshfegh AJ, Friday JE, Goldman JP, Ahuja JK. Presence of inulin and oligofructose in the diets of Americans. *J Nutr* 1999;**129**:S1407–11.

72. Schneeman BO. Fiber, inulin and oligofructoset: similarities and differences. *J Nutr* 1999; **129**:S1424–7.

73. Gibson GR, Beatty ER, Wang X, Cummings JH. Selective stimulation of bifidobacteria in the human colon by oligofructose and inulin. *Gastroenterology* 1995;**108**:975–82.

74. Clausen MR, Mortensen PB. Lactulose, disaccharides and colonic flora: clinical consequences. *Drugs* 1997; **53**:930–42.

75. Hidaka H, Eida T, Takizawa T, Tokunaga T, Tashiro Y. Effects of fructooligosaccharides on intestinal flora and human health. *Bifidobacteria Microflora* 1986;**5**:37–50.

76. Cherbut C. Inulin and oligofructose in the dietary fibre concept. *Br J Nutr* 2002;**87**(Suppl. 2):159–62.

77. Kleessen B, Sykura B, Zunft HJ, Blaut M. Effects of inulin and lactose on fecal microflora, microbial activity, bowel habit in elderly constipated persons. *Am J Clin Nutr* 1997;**65**:1397–402.

78. Holdstock DJ, Misiewicz JJ, Smith T. Propulsion (mass movement) in the human colon and its relationship to meals and somatic activity. *Gut* 1970;**11**:91–99.

79. Coenen C, Wegener M, Wedmann B, Schmidt G, Hoffmann S. Does physical exercise influence bowel transit time in healthy young men? *Am J Gastroenterol* 1992;**87**:292–5.

80. Keeling W, Martin BJ. Gastrointestinal transit during mild exercise. *J Appl Physiol* 1987;**63**:978–81.

81. Meshkinpour H, Selod S, Movahedi H, Nami N, James N, Wilson A. Effects of regular exercise in management of chronic idiopathic constipation. *Dig Dis Sci* 1998;**43**:2379–83.

82. Sikirov D. Comparison of straining during defecation in three positions: results and implications for human health. *Dig Dis Sci* 2003;**48**:1201–5.

83. Sirakov BA. Cardiovascular events at defecation: are they unavoidable? *Med Hypotheses* 1990;**32**:231–3.

84. Pendleton D, Schofield T, Tate P, Havelock P. *The new consultation. Developing doctor–patient communication*. Oxford: Oxford University Press; 2003.

85. Glasgow RE, La Chance PA, Toobert DJ, Brown J, Hampson SE, Riddle MC. Long-term effects and costs of brief behavioural dietary intervention for patients with diabetes delivered from the medical office. *Patient Educ Couns* 1997;**32**:175–84.

86. Eakin EG, Glasgow RE, Riley KM. Review of primary care-based physical activity intervention studies: effectiveness and implications for practice and future research. *J Fam Pract* 2000;**49**:158–68.

87. Brug J, van Assema P. Differences in use and impact of computer-tailored dietary fat-feedback according to stage of change and education. *Appetite* 2000;**34**:285–93.

88. Rollnick S, Miller WR. What is motivational interviewing? *Behav Cogn Psychother* 1995;**23**:325–34.

89. McGraw SA, Stone EJ, Osganian SK, Elder JP, Perry CL, Johnson CC, *et al.* Design of process evaluation within the Child and Adolescent Trial for Cardiovascular Health (CATCH). *Health Educ Q* 1994;**21**(Suppl. 2):5–26.

90. Oakley A, Strange V, Bonell C, Allen E, Stephenson J, RIPPLE Study Team. Process evaluation in randomised controlled trials of complex interventions. *BMJ* 2006;**332**:413–16.

91. May CR, Mair FS, Dowrick CF, Finch TL. Process evaluation for complex interventions in primary care: understanding trials using the normalization process model. *BMC Fam Pract* 2007;**8**:42.

92. Jolly K, Bradley F, Sharp S, Smith H, Thompson S, Kinmonth AL, *et al.* Randomised controlled trial of follow up care in general practice of patients with myocardial infarction and angina: final results of the Southampton heart integrated care project (SHIP). *BMJ* 1999;**318**:706–11.

93. Wiles R. Patients' perceptions of their heart attack and recovery: the influence of epidemiological "evidence" and personal experience. *Soc Sci Med* 1998;**46**:1477–86.

94. Jolly K, Lip GY, Sandercock J, Greenfield SM, Raftery JP, Mant J, *et al.* Home-based versus hospital-based cardiac rehabilitation after myocardial infarction or revascularisation: design and rationale of the Birmingham Rehabilitation Uptake Maximisation Study (BRUM): a randomised controlled trial [ISRCTN72884263]. *BMC Cardiovasc Disord* 2003;**3**:10.

95. May C, Ellis NT. When protocols fail: technical evaluation, biomedical knowledge, the social production of 'facts' about a telemedicine clinic. *Soc Sci Med* 2001;**53**:989–1002.

96. May C, Gask L, Atkinson T, Ellis N, Mair F, Esmail A. Resisting and promoting new technologies in clinical practice: the case of telepsychiatry. *Soc Sci Med* 2001;**52**:1889–901.

97. May CR, Mort M, Williams T, Mair F, Shaw NT. Understanding the evaluation of telemedicine: the play of the social and the technical, the shifting sands of reliable knowledge. Proceedings of the European Symposium on Information and Communication Technologies in Medicine, Rotterdam, 2001.

98. Mort M, May C, Williams T. Remote doctors and absent patients: acting at a distance in teledermatology. *Sci Technol Hum Value* 2003; **28**:274–95.

99. May C, Mort M, Williams T, Mair F, Gask L. Health Technology Assessment in its local contexts: studies of telehealthcare. *Soc Sci Med* 2003;**57**:697–710.

100. Woolf SH, Henshall C. Health technology assessment in the United Kingdom. *Int J Technol Assess Health Care* 2000;**16**:591–625.

101. Goodman CS, Ahn R. Methodological approaches of health technology assessment. *Int J Med Inform* 1999;**56**:97–105.

102. Pilgrim D, May C. Social scientists and the British National Health Service. *Soc Sci Health* 1998;**4**:42–54.

103. Gibbons M, Limoges C, Nowotny H, Schwartzman S, Scott P, Trow M. *The new production of knowledge*. London: Sage; 1994.

104. Tanenbaum SJ. Knowing and acting in medical research: the epistemological politics of outcomes research. *J Health Polit Policy Law* 1994;**19**:27–44.

105. Taylor FC, Davidson O, King M, Haines A, Davidson O, Sharp D. Recruitment of general practitioners to a randomized trial. *Br J Gen Pract* 1998;**48**:1704.

106. Ward E, King M, Lloyd M, Bower P, Friedli K. Conducting randomized trials in general practice: methodological and practical issues. *Br J Gen Pract* 1999;**49**:919–22.

107. Street A, Strong J, Karp S. Improving patient recruitment to multicentre clinical trials: the case for employing a data manager in a district general hospital-based oncology centre. *Clin Oncol* 2001;**13**:38–43.

108. Haidich AB, Ioannidis JPA. Patterns of patient enrolment in randomized controlled trials. *J Clin Epidemiol* 2001;**54**:877–83.

109. Sellors J, Cosby R, Trim K, Kaczorowski J, Howard M, Hardcastle L, *et al.* Recruiting family physicians and patients for a clinical trial: lessons learned. *Fam Pract* 2002;**19**:99–104.

110. Allsup SJ, Gosney MA. Difficulties of recruitment for a randomized controlled trial involving influenza vaccination in healthy older people. *Gerontology* 2002;**48**:170–3.

111. Shelton BJ, Wofford JL, Gosselink CA, McClatchey MW, Brekke K, Conry C, *et al.* Recruitment and retention of physicians for primary care research. *J Community Health* 2002;**27**:79–89.

112. Lehoux P, Blume S. Technology assessment and the sociopolitics of health technologies. *J Health Polit Policy Law* 2000;**25**:1083–120.

113. Schwartz D, Lellouch J. Explanatory and pragmatic attitudes in therapeutical trials. *J Chronic Dis* 1967;**20**:637–48.

114. Tramonte SM, Brand MB, Mulrow CD, Amato MG, O'Keefe ME, Ramirez G. The treatment of chronic constipation in adults: a systematic review. *J Gen Intern Med* 1997;**12**:15–24.

115. Kristal AR, Curry SJ, Shattuck AL, Feng Z, Li S. A randomized trial of a tailored, self-help dietary intervention: the Puget Sound Eating Patterns study. *Prev Med* 2000;**31**:380–9.

116. Lutz SF, Ammerman AS, Atwood JR, Campbell MK, DeVellis RF, Rosamond WD, *et al.* Innovative newsletter interventions improve fruit and vegetable consumption in healthy adults. *J Am Diet Assoc* 1999;**99**:705–9.

117. Bandura A. Self-efficacy: toward a unifying theory of behavioural change. *Psychol Rev* 1977;**84**:191–215.

118. Prochaska JO, DiClemente CC. Preparing people to change addictive behaviour. In Miller W, Rollnick S, editors. *Toward a comprehensive model of change, in motivational interviewing.* London: Gilford Press; 1991. pp. 3–27.

119. Lake AA, Speed C, Brookes A, Heaven B, Adamson AJ, Moynihan P, *et al.* Development of a series of patient information leaflets for constipation using a range of cognitive interview techniques: LIFELAX. *BMC Health Serv Res* 2007;**7**:3.

120. Veldhuyzen van Zanten SJ, Talley NJ, Bytzer P, Klein KB, Whorwell PJ, Zinsmeister AR. Design of treatment trials for functional gastrointestinal disorders. *Gut* 1999;**45**(Suppl. II):1169–77.

121. Cadman L. Bite-size training. *Pract Nurse* 1996;**17**:607–9.

122. Thompson WG, Longstreth GF, Drossman DA, Heaton KW, Irvine EJ, Müller-Lissner SA. Functional bowel disorders and functional abdominal pain. *Gut* 1999;**45**(Suppl. 2):43–7.

123. Schaefer DC, Cheskin LJ. Constipation in the elderly. *Am Fam Physician* 1998;**58**:907–14.

124. British Medical Association and Royal Pharmaceutical Society of Great Britain. *British national formulary.* No. 41. 2001, London: BMA and RPS.

125. Donner AN, Klar N. *Design and analysis of cluster randomization trials in health research*. London: Arnold; 2000.

126. Liang MH, Fossel AH, Larson MG. Comparisons of five health status instruments for orthopedic evaluation. *Med Care* 1990;**28**:632–42.

127. Frank L, Kleinman L, Farup C, Taylor L, Miner P Jr. Psychometric validation of a constipation symptom assessment questionnaire. *Scand J Gastroenterol* 1999;**34**:870–7.

128. Brooks RG. EuroQol: the current state of play. *Health Policy* 1996;**37**:53–72.

129. EuroQol Group. A new facility for the measurement of health related quality of life. *Health Policy* 1990;**16**:199–208.

130. Zigmond AS, Snaith RP. The hospital anxiety and depression scale. *Acta Psychiatr Scand* 1983;**67**:361–70.

131. MRC CFAS Medical Research Council Cognitive Function and Ageing Study Group. The description of activities of daily living in five centres in England and Wales. *Age Ageing* 1998;**27**:605–13.

132. Davison J, Bond J, Dawson P, Steen IN, Kenny RA. Patients with recurrent falls attending Accident & Emergency benefit from multifactorial intervention: a randomised controlled trial. *Age Ageing* 2005;**34**:162–8.

133. Shaw FE, Bond J, Richardson DA, Dawson P, Steen IN, McKeith IG, *et al.* Multifactorial intervention after a fall in older people with cognitive impairment and dementia presenting to the accident and emergency department: randomised controlled trial. *BMJ* 2003;**326**:73–5.

134. Eccles M, Grimshaw J, Steen N, Parkin D, Purves I, McColl E, *et al.* The design and analysis of a randomized controlled trial to evaluate computerized decision support in primary care: the COGENT study. *Fam Pract* 2000;**17**:180–6.

135. Eccles M, McColl E, Steen N, Rousseau N, Grimshaw J, Parkin D, *et al.* Effect of computerised evidence based guidelines on management of asthma and angina in adults in primary care: cluster randomised controlled trial. *BMJ* 2002;**325**:941–4.

136. Mauskopf JA, Paul JE, Grant DM, Stergachis A. The role of cost-consequence analysis in healthcare decision-making. *Pharmacoeconomics* 1998;**13**:277–88.

137. May C. A rational model for assessing and evaluating complex interventions in health care. *BMC Health Serv Res* 2006;**6**(86).

138. Glaser BG, Strauss A. *The discovery of grounded theory*. Chicago, IL: Aldine; 1967.

139. Roe L, Strong C, Whiteside C, Neil A, Mant D. Dietary intervention in primary care: validity of the DINE method for diet assessment. *Fam Pract* 1994;**11**:375–81.

140. Roe L, Hunt P, Bradshaw H. *Health promotion interventions to promote healthy eating in the general population: a review*. London: Health Education Authority; 1997.

141. Riemsma RP, Pattenden J, Bridle C, Sowden AJ, Mather L, Watt IS, *et al.* A systematic review of the effectiveness of interventions based on a stages-of-change approach to promote individual behaviour change. *Health Technol Assess* 2002;**6**(24).

142. Shinitzhy HE, Kub J. The art of motivating behaviour change: the use of motivational interviewing to promote health. *Public Health Nurs* 2001;**18**:178–85.

143. Simons-Morton DG, Calfas KJ, Oldenburg B, Burton NW. Effects of interventions in health care settings on physical activity or cardiorespiratory fitness. *Am J Prev Med* 1998; **15**:413–30.

144. Marcus BH, Banspach SW, Lefebvre RC, Rossi JS, Carleton RA, Abrams DB. Using the Stages of Change Model to increase the adoption of physical activity among community participants. *Am J Health Promot* 1992;**6**:424–9 (p. 426 missing).

145. Marcus BH, Bock BC, Pinto BM, Forsyth LH, Roberts MB, Traficante RM. Efficacy of an individualized, motivationally-tailored physical activity intervention. *Ann Behav Med* 1998;**20**:174–80.

146. Hillsdon M, Thorogood M, White I, Foster C. Advising people to take more exercise is ineffective: a randomized controlled trial of physical activity promotion in primary care. *Int J Epidemiol* 2002;**31**:808–15.

147. Fletcher A, Rake C. Effectiveness of interventions to promote healthy eating in elderly people living in the community: a review. London: Health Education Authority; 1998.

148. Pereira Gray D. Forty-seven minutes a year for the patient. *Br J Gen Pract* 1998; **48**:1816–17.

149. Horrocks S, Anderson E, Salisbury C. Systematic review of whether nurse practitioners working in primary care can provide equivalent care to doctors. *BMJ* 2002; **324**:819–23.

150. Shum C, Humphreys A, Wheeler D, Cochrane MA, Skoda S, Clement S. Nurse management of patients with minor illnesses in general practice: multicentre, randomised controlled trial. *BMJ* 2000;**320**:1038–43.

151. Kinnersley P, Anderson E, Parry K, Clement J, Archard L, Turton P, *et al.* Randomised controlled trial of nurse practitioner versus general practitioner care for patients requesting 'same day' consultations in primary care. *BMJ* 2000;**320**:1043–8.

152. Truswell AS. Family physicians and patients: is effective nutrition interaction possible? *Am J Clin Nutr* 2000; **71**:6–12.

153. US Preventive Services Task Force. Behavioral counseling in primary care to promote a healthy diet: recommendations and rationale. *Am J Prev Med* 2003;**24**:93–100.

154. Ashenden RC, Silagy D, Weller A. systematic review of the effectiveness of promoting lifestyle change in general practice. *Fam Pract* 1997;**14**:160–76.

155. Nicholas LG, Pond CD, Roberts DCK. Dietitian: general practitioner interface: a pilot study on what influences the provision of effective nutrition management. *Am J Clin Nutr* 2003;**77**(Suppl.):1039–42.

156. Kushner RF. Barriers to providing nutrition counseling by physicians: a survey of primary care practitioners. *Prev Med* 1995;**24**:546–52.

157. Butler C, Rollnick S, Stott N. The practitioner, the patient and resistance to change: recent ideas on compliance. *CMAJ* 1996;**154**:1357–62.

158. Abraham C, Michie S. A taxonomy of behaviour change techniques used in interventions. *Health Psychol* 2008;**27**:379–87.

159. Kreuter MW, Strecher VJ, Glassman B. One size does not fit all: the case for tailoring print materials. *Ann Behav Med* 1999;**21**:276–83.

160. Skinner CS, Campbell MK, Rimer BK, Curry S, Prochaska JO. How effective is tailored print communication? *Ann Behav Med* 1999;**21**:290–8.

161. Britt E, Hudson SM, Blampied NM. Motivational interviewing in health settings: a review. *Patient Educ Couns* 2003;**53**:147–155.

162. Rollnick SW, Miller R. What is motivational interviewing? *Behav Cogn Psychother* 1995;**23**:325–34.

163. Miller WR, Rollnick S. *Motivational interviewing. Preparing people for change*. 2nd edn. New York, NY: Gilford Press; 2002.

164. Prochaska JO, DiClemente CC. Toward a comprehensive model of change. In Miller WR, Heather N, editors. *Treating addictive behaviours: processes of change*. New York, NY: Plenum Press, 1986; pp. 3–27.

165. Prochaska J, DiClemente C. Stages and processes of self change of smoking: toward an integrative model of change. *J Consult Clin Psychol* 1983;**51**:390–5.

166. Rollnick S, Kinnersley P, Stott N. Methods of helping patients with behaviour change. *BMJ* 1993;**307**:188–90.

167. Emmons KM, Rollnick S. Motivational interviewing in health care settings. Opportunities and limitations. *Am J Prev Med* 2001;**20**:68–74.

168. Burke BL, Arkowitz H, Dunn C. The efficacy of motivational interviewing and its adaptations. What we know so far. In Miller WR, Rollnick S, editors. *Motivational interviewing. Preparing people for change*. New York, NY: Guilford Press; 2002.

169. Dunn C, Deroo L, Rivara FP. The use of brief interventions adapted from motivational interviewing across behavioral domains: a systematic review. *Addiction* 2001;**96**:1725–42.

170. Resnicow K, DiIorio C, Soet J. Motivational interviewing in medical and public health settings. In Miller WR, Rollnick S, editors. *Motivational interviewing. Preparing people for change*. New York, NY: Guilford Press; 2002. pp. 251–69.

171. Ondersma SJ, Chase SK, Svikis DS, Schuster CR. Computer-based brief motivational intervention for perinatal drug use. *J Subst Abuse Treat* 2005;**28**:305–12.

172. Berg-Smith SM, Stevens VJ, Brown KM, Van Horn L, Gernhofer N, Peters E, *et al.* A brief motivational intervention to improve dietary adherence in adolescents. *Health Educ Res* 1999;**14**:399–410.

173. Humfress H, Igel V, Lamont A, Tanner M, Morgan J, Schmidt U. The effect of a brief motivational intervention on community psychiatric patients' attitudes to their care, motivation to change, compliance and outcome: A case control study. *J Ment Health* 2002;**11**:155–66.

174. Miller WR, Motivational interviewing: research, practice and puzzles. *Addict Behav* 1996;**21**:835–42.

175. Rollnick S, Heather N, Bell A. Negotiating behaviour change in medical settings: The development of brief motivational interviewing. *J Ment Health* 1992;**1**:25–37.

176. Rollnick S, Heather N, Gold R, Hall W. Development of short 'readiness to change' questionnaire for use in brief, opportunistic interventions among excessive drinkers. *Br J Addict* 1992;**87**:743–54.

177. Stott NC, Rollnick S, Rees MR, Pill RM. Innovation in clinical method: diabetes care and negotiating skills. *Fam Pract* 1995;**12**:413–18.

178. Stott NC, Rees M, Rollnick S, Pill RM, Hackett P. Professional responses to innovation in clinical method: diabetes care and negotiating skills. *Patient Educ Couns* 1996;**29**:67–73.

179. Bandura A. *Self-efficacy: the exercise of control*. New York, NY: Freeman; 1994.

180. Rollnick S, Butler CC, Stott N. Helping smokers make decisions: enhancement of brief intervention for general medical practice. *Patient Educ Couns* 1997;**31**:191–203.

181. Pignone MP, Ammerman A, Fernandez L, Orleans CT, Pender N, Woolf S, *et al.* Counseling to promote a healthy diet in adults. *Am J Prev Med* 2003;**24**:75–92.

182. Ammerman A, Pignone MP, Fernandez L. Counselling to promote a healthy diet. Systematic evidence review no. 18. 2002. URL: www.ahrq.gov/clinic/serfiles.htm (cited 2003).

183. Steptoe A, Doherty S, Rink E, Kerry S, Kendrick T, Hilton S. Behavioural counselling in general practise for the promotion of healthy behaviour among adults at increased risk of coronary heart disease: randomised trial. *BMJ* 1999;**319**:943–8.

184. Rollnick S, Mason P, Butler C. *Health behaviour change. A guide for practitioners*. Edinburgh: Churchill Livingstone; 2002.

185. Stewart M, Brown JB, Weston WW, McWhinney IR, McWilliam CL, Freeman TR. *Patient-centred medicine: transforming the clinical method*. Thousand Oaks, CA: SAGE; 1995.

186. Cambridge University Press. *Cambridge dictionaries online*. URL: http://dictionary.cambridge.org/ (cited 16 April 2004).

187. Salmon P, Peters S, Rogers A, Gask L, Clifford R, Iredale W, *et al.* Peering through the barriers in GPs' explanations for declining to participate in research: the role of professional autonomy and the economy of time. *Fam Pract* 2007;**24**:269–75.

188. Mant D. R&D in primary care: an NHS priority. *Br J Gen Pract* 1998;**48**:871.

189. Speed C. Site-specific assessments: yet another barrier to research. *BMJ* 2004;**329**:282–4.

190. Lecouturier J, Bamford C, Foy R, Eccles M. Did changes in the NHS guidance and application procedures shorten time taken for research governance approval? NoReN (Northern Primary Care Research Network), Annual Research Presentation Day, Collingwood College, Durham, 2005.

191. Rowe JC, Elling ME, Hazlewood JG, Zakhary R. A cure for clinical trials. *McKinsey Quarterly* 2002;**2**:134–41.

192. Farrell B. Efficient management of randomised controlled trials: nature or nurture. *BMJ* 1998;**317**:1236–9.

193. Campbell MK, Snowdon C, Francis D, Elbourne D, McDonald AM, Knight R, *et al.* Recruitment to randomised trials: strategies for trial enrollment and participation study. The STEPS study. *Health Technol Assess* 2007;**11**(48).

194. Francis D, Roberts I, Elbourne DR, Shakur H, Knight RC, Garcia J, *et al.* Marketing and clinical trials: a case study. *Trials* 2007;**8**:37.

195. Nelson M. Recruitment in primary care research. Primary Care Alliance for Clinical Trials (PACT). *Aust Fam Physician* 2004;**33**:1039–40.

196. Gabbay M, Thomas J. When free condoms and spermicide are not enough: barriers and solutions to participant recruitment to community-based trials. *Control Clin Trials* 2004;**25**:388–99.

197. Foy R, Parry J, Duggan A, Delaney B, Wilson S, Lewin-Van Den Broek NT, *et al.* How evidence based are recruitment strategies to randomized controlled trials in primary care? Experience from seven studies. *Fam Pract* 2003;**20**:83–92.

198. House of Commons Social Security Committee. *The Royal Liverpool children's inquiry report*. London: HMSO; 2001.

199. *Human Rights Act*. London: HMSO; 1998.

200. Department of Health. *Research governance framework for health and social care*. London: Department of Health; 2001.

201. Dumville JC, Watson J, Raynor P, Torgerson DJ. Research governance: a barrier to ethical research? *Q JM* 2004; **97**:113–14.

202. Ewing G, Rogers M, Barclay S, McCabe J, Martin A, Todd C. Recruiting patients into a primary care based study of palliative care: why is it so difficult? *Palliat Med* 2004; **18**:452–9.

203. Salisbury C, Leese B, McManus RJ. Ensuring that research governance supports rather than stifles research. *Br J Gen Pract* 2005;**55**:4–5.

204. Hewison J, Haines A. Overcoming barriers to recruitment in health research. *BMJ* 2006;**333**:300–2.

205. Angus VC, Entwistle VA, Emslie MJ, Walker KA, Andrew JE. The requirement for prior consent to participate on survey response rates: a population based survey in Grampian. *BMC Health Serv Res* 2003;**3**:21.

206. McColl E, Lecoutrier J, Corbett S, Speed C, Vanoli A, Welfare M. *Self-management in ulcerative colitis: a report of a randomised controlled trial with economic evaluation and qualitative assessment*.

Centre for Health Services Research, University of Newcastle upon Tyne and Northumbria Healthcare NHS Trust, Newcastle upon Tyne, 2003.

207. Zigmond AS, Snaith RP. The hospital anxiety and depression scale. *Acta Psychiatr Scand* 1983;**67**:361–70.

208. Cronbach L. Coefficient alpha and the internal structure of tests. *Psychometrika* 1951;**16**:287–334.

209. Garvey M, Noyes Jr R, Yates W. Frequency of constipation in major depression: relationship to other clinical variables. *Psychosomatics* 1990;**31**:204–6.

210. Gorard DA, Gomborone JE, Libby GW, Farthing MJ. Intestinal transit in anxiety and depression. *Gut* 1996;**39**:551–5.

211. Drummond M, Stoddard GL, Torrance GW. *Methods for the economic analysis of health care programmes*. Oxford: Oxford University Press; 1987.

212. The EuroQol Group. EuroQol: a new facility for the measurement of health related quality of life. *Health Policy* 1990;**16**:199–208.

213. Dolan P. Modeling Valuations for EuroQol Health States. *Med Care* 1997;**35**:1095–108.

214. Department of Health. *Research governance framework for health and social care*. London: Department of Health; 2005.

215. Wald DS. Bureaucracy of ethics applications. *BMJ* 2004;**329**:282–4.

216. Speed C. Site-specific assessments: yet another barrier to research. Rapid response to: David S Wald, Bureaucracy of Ethics Applications. *BMJ* 2004;**329:**282–4.

217. Levine RJ. Clinical trials and physicians as double agents. *Yale J Biol Med* 1992;**65**:65–74.

218. Prout H, Butler C, Kinnersley P, Robling M, Hood K, Tudor-Jones R. A qualitative evaluation of implementing a randomised controlled trial in general practice. *Fam Pract* 2003;**20**:675–81.

219. Salmon P, Peters S, Rogers A, Gask L, Clifford R, Iredale W, *et al.* Peering through the barriers in GPs' explanations for declining to participate in research: the role of professional autonomy and the economy of time. *Fam Pract* 2007;**24**:269–75.

220. Ross S, Grant A, Counsell C, Gillespie W, Russell I, Prescott R. Barriers to participation in randomised controlled trials: a systematic review. *J Clin Epidemiol* 1999;**52**:1143–56.

221. Viner R. Transition from paediatric to adult care. Bridging the gaps or passing the buck? *Arch Dis Child* 1999;**81**:271–5.

222. Strauss AL. *Social organization of medical work*. Chicago, IL: University of Chicago Press; 1985.

223. Heaven B, Murtagh M, Rapley T, May C, Graham R, Kaner E, *et al.* Patients or research subjects? A qualitative study of participation in a randomised controlled trial of a complex intervention. *Patient Educ Couns* 2006;**62**:260–70.

224. Morris N, Bàlmer B. Volunteer human subjects' understandings of their participation in a biomedical research experiment. *Soc Sci Med* 2006;**62**:998–1008.

225. Wager E, Tooley PJ, Emanuel MB, Wood SF. How to do it: get patients' consent to enter clinical trials. *BMJ* 1995;**311**:734–7.

226. Snowdon C, Garcia J, Elbourne D. Making sense of randomization: responses of parents of critically ill babies to random allocation of treatment in a clinical trial. *Soc Sci Med* 1997;**45**:1337–55.

227. Joffe S, Cook EF, Cleary PD, Clark JW, Weeks JC. Quality of informed consent: a new measure of understanding among research subjects. *J Natl Cancer Inst* 2001;**93**:139–47.

228. Campbell M, Fitzpatrick R, Haines A, Kinmonth AL, Sandercock P, Spiegelhalter D, *et al.* Framework for design and evaluation of complex interventions to improve health. *BMJ* 2000;**321**:694–6.

229. Featherstone K. The experience of trial participation. *J Rheumatol* 2003;**30**:646–7.

230. Featherstone K, Donovan JL. Random allocation or allocation at random? Patients' perspective of participation in a randomised controlled trial. *BMJ* 1998;**317**:1180.

231. Featherstone K, Donovan JL. 'Why don't they just tell me straight, why allocate it?' The struggle to make sense of participating in a randomised controlled trial. *Soc Sci Med* 2002;**55**:709–19.

232. McDonald AM, Knight RC, Campbell MK, Entwistle VA, Grant AM, Cook JA, *et al.* What influences recruitment to randomised controlled trials? A review of trials funded by two UK funding agencies. *Trials* 2006;**7**:9.

233. May C. A rational model for assessing and evaluating complex interventions in health care. *BMC Health Serv Res* 2006;**6**:86.

Appendix 1
Protocols

LIFELAX protocol, version 2 (18 February 2004)

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 Northern England and the homes of older people (aged 55 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 (a separate, but parallel, trial (STOOL) by the same research team is comparing stimulant, bulk and osmotic laxative, singly and in combination). 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 be have on-site training in patient recruitment and the treatment protocol. In addition, a dietician with experience in health promotion will deliver in-practice training in 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 or district nurses 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 55 or over with chronic constipation living in private households. The choice of an age cut-off of people aged 55 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. Patients identified through the electronic query will be invited to attend a recruitment clinic at their general practice, at 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)

Patients identified through the electronic query as meeting initial eligibility criteria will be invited to attend a nurse-led recruitment clinic. At this clinic, 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. The study will be explained and a baseline questionnaire to assess activities of daily living[29], condition-specific quality of life and laxative use (both prescribed and over the counter) will be administered. A weekly structured self-completed diary will be distributed and explained. Informed consent will be taken at this recruitment clinic. An invitation to return to a week later, to initiate treatment per intervention protocol (1.3.5.4) will be issued. Should patients decide to withdraw when they return to collect either their laxative prescription or for their diet and lifestyle appointment, baseline interview and questionnaire data will be destroyed.

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 telephone call 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 by practice (facilitated by research team) to patient to attend nurse-led clinic to discuss constipation.
4	W^{0}	Nurse-led clinic – eligibility confirmed; consent for data collection obtained; base-line assessment; diary issued and explained; follow-up appointment arranged for a week later;
5	W^{1}	Nurse-led clinic – laxative prescription issued or diet and lifestyle intervention initiated. Baseline data destroyed if patient wishes to withdraw.
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 telephone call 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 the Northern England 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 eligibility 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.

(In the parallel STOOL study, we will also seek to develop scenarios based on symptoms of constipation and condition-specific quality of life, and to use standard gamble and time trade-off techniques to establish utilities for the defined health states. The findings from this work could also be applied in the LIFELAX trial).

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 the Northern and Yorkshire 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

1. Glasgow RE, La Chance PA, Toobert DJ, Brown J, Hampson SE, Riddle MC. Long-term effects and costs of brief behavioural dietary intervention for patients with diabetes delivered from the medical office. *Patient Education & Counseling* 1997;**32**:175-184.

2. Brug J, van Assema P. Differences in use and impact of computer-tailored dietary fat-feedback according to stage of change and education. *Appetite* 2000;**34**:285-293.

3. Eakin EG, Glasgow RE, Riley KM. Review of primary care-based physical activity intervention studies: effectiveness and implications for practice and future research. [see comments]. [Review] [51 refs]. *Journal of Family Practice* 2000;**49**:158-168.

4. Prochaska JO, DiClemente CC. Toward a comprehensive model of change. In Miller W, Rollnick S, eds. *Motivational Interviewing: preparing people to change addictive behaviour*, pp 3-27. London: Gilford Press, 1991.

5. Rollnick S, Miller WR. What is motivational interviewing? *Behavioural and Cognitive Psychotherapy* 1995;**23**:325-334.

6. Lutz SF, Ammerman AS, Atwood JR, Campbell MK, DeVellis RF, Rosamond WD. Innovative newsletter interventions improve fruit and vegetable consumption in healthy adults. *Journal of the American Dietetic Association* 1999;**99**:705-709.

7. Kristal AR, Curry SJ, Shattuck AL, Feng Z, Li S. A randomized trial of a tailored, self-help dietary intervention: the Puget Sound Eating Patterns study. *Preventive Medicine* 2000;**31**:380-389.

8. Schwartz D, Lellouch J. Explanatory and pragmatic attitudes in therapeutical trials. *J Chron Dis* 1967;**20**:637-648.

9. Donner A. Some aspects of the design and analysis of cluster randomization trials. *Applied Statistics* 1998;**47**:95-113.

10. Petticrew M, Watt I, Sheldon T. Systematic review of the effectiveness of laxatives in the elderly. *Health Technology Assessment* 1997;**1**.

11. Tramonte SM, Brand MB, Mulrow CD, Amato MG, O'Keefe ME, Ramirez G. The treatment of chronic constipation in adults. A systematic review. [see comments]. *Journal of General Internal Medicine* 1997;**12**:15-24.

12. Bandura A. Self-efficacy: towards a unifying theory of behaviour change. *Psychological Review* 1977;**84**:191-215.

13. Stephen AM, Cummings JH. Mechanism of action of dietary fibre on the human colon. *Nature* 1980;**284**:283-284.

14. Sandman PO, Adolfsson R, Hallmans G, Nygren C, Nystrom L, Winblad B. Treatment of constipation with high-bran bread in long-term care of severely demented elderly patients. *Journal of the American Geriatrics Society* 1983;**31**:289-293.

15. Anti M, Pignataro G, Armuzzi A, Valenti A, Iascone E, Marmo R *et al*. Water supplementation enhances the effect of high-fiber diet on stool frequency and laxative consumption in adult patients with functional constipation. *Hepato-Gastroenterology* 1998;**45**:727-732.

16. Moynihan PJ, Snow S, Jepson NJ, Butler TJ. The intake of non-starch polysaccharide (dietary fibre) in edentulous and dentate persons: an observational study. *British Dental Journal* 1994;**177**:243-247.

17. Benton JM, O'Hara PA, Chen H, Harper DW, Johnston SF. Changing bowel hygiene practice successfully: a program to reduce laxative use in a chronic care hospital. *Geriatric Nursing* 1997;**18**:12-17.

18. Resende TL, Brocklehurst JC, O'Neill PA. A pilot study on the effect of exercise and abdominal massage on bowel habit in continuing care patients. *Clinical Rehabilitation, 7(3):204.-9,* 1993.

19. Lederle FA. Epidemiology of constipation in elderly patients. Drug utilisation and cost-containment strategies. [Review] [27 refs]. *Drugs & Aging* 1995;**6**:465-469.

20. Cadman L. Bite-size training. *Practice Nurse* 1996;**17**:607-609.

21. McCormick A, Fleming D, Charlton J. Morbidity statistics from general practice: fourth national study. OPCS: London, 1995.

22. Thompson WG, Longstreth GF, Drossman DA, Heaton KW, Irvine EJ, Müller-Lissner SA. Functional bowel disorders and functional abdominal pain. *Gut* 1999;**45**:43-47.

23. Schaefer DC, Cheskin LJ. Constipation in the elderly. [Review] [17 refs]. *American Family Physician* 1998;**58**:907-914.

24. Joint Formulary Committee. British National Formulary No 41. London: British Medical Association and Royal Pharmaceutical Society of Great Britain, 2001.

25. Frank L, Kleinman L, Farup C, Taylor L, Miner P, Jr. Psychometric validation of a constipation symptom assessment questionnaire. *Scandinavian Journal of Gastroenterology* 1999;**34**:870-877.

26. EuroQol Group. Euroqol - a new facility for the measurement of health related quality of life. *Health Pol* 1990;**16**:199-208.

27. Brooks R. Euroqol - the current state of play. *Health Pol* 1996;**37**:53-72.

28. Zigmond AS, Snaith RP. The hospital anxiety and depression scale. *Acta Psychiatr Scand* 1983;**67**:361-370.

29. MRC CFAS Medical Research Council Cognitive Function and Ageing Study Group. The description of activities of daily living in five centres in England and Wales. *Age Ageing* 1998;**27**:605-613.

30. McColl E, Jacoby A, Thomas L, Soutter J, Bamford C, Steen N *et al*. The conduct and design of questionnaire surveys in healthcare research. In Stevens A, Abrams K, Brazier J, Fitzpatrick R, Lilford R, eds. *The Advanced Handbook of Methods in Evidence Based Healthcare*, pp 247-271. London: Sage, 2001.

31. Donner A, Klar N. Design and analysis of cluster randomization trials in health research. London: Arnold, 2000.

32. Liang MH, Fossel AH, Larson MG. Comparisons of five health status instruments for orthopedic evaluation. *Med Care* 1990;**28**:632-642.

33. Mauskopf JA, Paul JE, Grant DM, Stergachis A. The role of cost-consequence analysis in healthcare decision-making. *Pharmacoeconomics* 1998;**13**:277-288.

34. Netten A, Curtis L. Unit costs of health and social care 2000. Canterbury: Personal Social Services Research Unit, 2000.

35. Hutton JL. Are distinctive ethical principles required for cluster randomized controlled trials? *Statistics in Medicine* 2001;**20**:473-488.

LIFELAX protocol, version 5 (24 July 2006)

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

1. Glasgow RE, La Chance PA, Toobert DJ, Brown J, Hampson SE, Riddle MC. Long-term effects and costs of brief behavioural dietary intervention for patients with diabetes delivered from the medical office. *Patient Education & Counseling* 1997;**32**:175-184.

2. Brug J, van Assema P. Differences in use and impact of computer-tailored dietary fat-feedback according to stage of change and education. *Appetite* 2000;**34**:285-293.

3. Eakin EG, Glasgow RE, Riley KM. Review of primary care-based physical activity intervention studies: effectiveness and implications for practice and future research. [see comments]. [Review] [51 refs]. *Journal of Family Practice* 2000;**49**:158-168.

4. Prochaska JO, DiClemente CC. Toward a comprehensive model of change. In Miller W, Rollnick S, eds. *Motivational Interviewing: preparing people to change addictive behaviour*, pp 3-27. London: Gilford Press, 1991.

5. Rollnick S, Miller WR. What is motivational interviewing? *Behavioural and Cognitive Psychotherapy* 1995;**23**:325-334.

6. Lutz SF, Ammerman AS, Atwood JR, Campbell MK, DeVellis RF, Rosamond WD. Innovative newsletter interventions improve fruit and vegetable consumption in healthy adults. *Journal of the American Dietetic Association* 1999;**99**:705-709.

7. Kristal AR, Curry SJ, Shattuck AL, Feng Z, Li S. A randomized trial of a tailored, self-help dietary intervention: the Puget Sound Eating Patterns study. *Preventive Medicine* 2000;**31**:380-389.

8. Schwartz D, Lellouch J. Explanatory and pragmatic attitudes in therapeutical trials. *J Chron Dis* 1967;**20**:637-648.

9. Donner A. Some aspects of the design and analysis of cluster randomization trials. *Applied Statistics* 1998;**47**:95-113.

10. Petticrew M, Watt I, Sheldon T. Systematic review of the effectiveness of laxatives in the elderly. *Health Technology Assessment* 1997;**1**.

11. Tramonte SM, Brand MB, Mulrow CD, Amato MG, O'Keefe ME, Ramirez G. The treatment of chronic constipation in adults. A systematic review. [see comments]. *Journal of General Internal Medicine* 1997;**12**:15-24.

12. Bandura A. Self-efficacy: towards a unifying theory of behaviour change. *Psychological Review* 1977;**84**:191-215.

13. Stephen AM, Cummings JH. Mechanism of action of dietary fibre on the human colon. *Nature* 1980;**284**:283-284.

14. Sandman PO, Adolfsson R, Hallmans G, Nygren C, Nystrom L, Winblad B. Treatment of constipation with high-bran bread in long-term care of severely demented elderly patients. *Journal of the American Geriatrics Society* 1983;**31**:289-293.

15. Anti M, Pignataro G, Armuzzi A, Valenti A, Iascone E, Marmo R *et al*. Water supplementation enhances the effect of high-fiber diet on stool frequency and laxative consumption in adult patients with functional constipation. *Hepato-Gastroenterology* 1998;**45**:727-732.

16. Moynihan PJ, Snow S, Jepson NJ, Butler TJ. The intake of non-starch polysaccharide (dietary fibre) in edentulous and dentate persons: an observational study. *British Dental Journal* 1994;**177**:243-247.

17. Benton JM, O'Hara PA, Chen H, Harper DW, Johnston SF. Changing bowel hygiene practice successfully: a program to reduce laxative use in a chronic care hospital. *Geriatric Nursing* 1997;**18**:12-17.

18. Resende TL, Brocklehurst JC, O'Neill PA. A pilot study on the effect of exercise and abdominal massage on bowel habit in continuing care patients. *Clinical Rehabilitation, 7(3):204.-9,* 1993.

19. Lederle FA. Epidemiology of constipation in elderly patients. Drug utilisation and cost-containment strategies. [Review] [27 refs]. *Drugs & Aging* 1995;**6**:465-469.

20. Cadman L. Bite-size training. *Practice Nurse* 1996;**17**:607-609.

21. McCormick A, Fleming D, Charlton J. Morbidity statistics from general practice: fourth national study. OPCS: London, 1995.

22. Thompson WG, Longstreth GF, Drossman DA, Heaton KW, Irvine EJ, Müller-Lissner SA. Functional bowel disorders and functional abdominal pain. *Gut* 1999;**45**:43-47.

23. Schaefer DC, Cheskin LJ. Constipation in the elderly. [Review] [17 refs]. *American Family Physician* 1998;**58**:907-914.

24. Joint Formulary Committee. British National Formulary No 41. London: British Medical Association and Royal Pharmaceutical Society of Great Britain, 2001.

25. Frank L, Kleinman L, Farup C, Taylor L, Miner P, Jr. Psychometric validation of a constipation symptom assessment questionnaire. *Scandinavian Journal of Gastroenterology* 1999;**34**:870-877.

26. EuroQol Group. Euroqol - a new facility for the measurement of health related quality of life. *Health Pol* 1990;**16**:199-208.

27. Brooks R. Euroqol - the current state of play. *Health Pol* 1996;**37**:53-72.

28. Zigmond AS, Snaith RP. The hospital anxiety and depression scale. *Acta Psychiatr Scand* 1983;**67**:361-370.

29. MRC CFAS Medical Research Council Cognitive Function and Ageing Study Group. The description of activities of daily living in five centres in England and Wales. *Age Ageing* 1998;**27**:605-613.

30. McColl E, Jacoby A, Thomas L, Soutter J, Bamford C, Steen N *et al*. The conduct and design of questionnaire surveys in healthcare research. In Stevens A, Abrams K, Brazier J, Fitzpatrick R, Lilford R, eds. *The Advanced Handbook of Methods in Evidence Based Healthcare*, pp 247-271. London: Sage, 2001.

31. Donner A, Klar N. Design and analysis of cluster randomization trials in health research. London: Arnold, 2000.

32. Liang MH, Fossel AH, Larson MG. Comparisons of five health status instruments for orthopedic evaluation. *Med Care* 1990;**28**:632-642.

33. Mauskopf JA, Paul JE, Grant DM, Stergachis A. The role of cost-consequence analysis in healthcare decision-making. *Pharmacoeconomics* 1998;**13**:277-288.

34. Netten A, Curtis L. Unit costs of health and social care 2000. Canterbury: Personal Social Services Research Unit, 2000.

35. Hutton JL. Are distinctive ethical principles required for cluster randomized controlled trials? *Statistics in Medicine* 2001;**20**:473-488.

Appendix 2

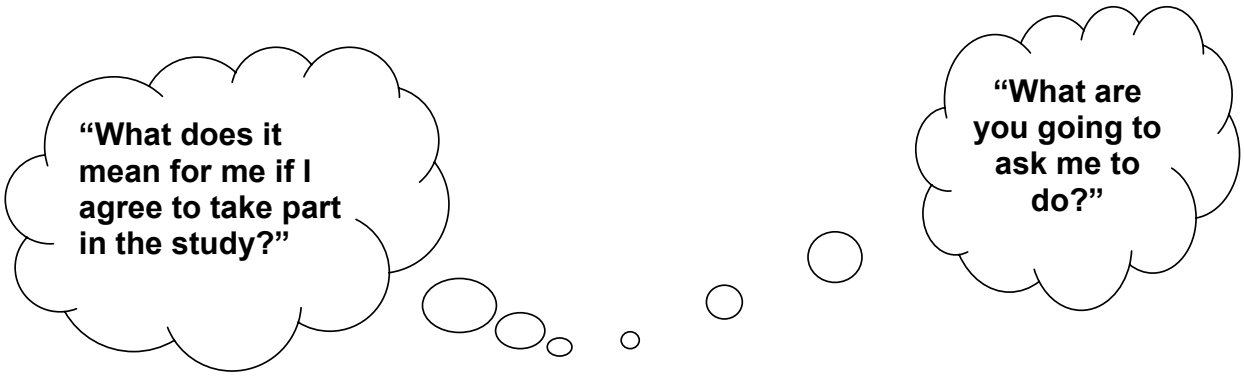
Patient information sheets

LIFELAX brief patient info sheet (PIS), version 5 (26 May 2006)

ISRCTN7388134

UNIVERSITY OF NEWCASTLE UPON TYNE

lifelax



A study about different ways of treating constipation in older people

Diet and lifestyle versus laxatives in the management of chronic constipation in older people.

Some important questions answered

Welcome to LIFELAX. We would like to invite you to take part in our research study. This study looks at the way that constipation in older people is treated by doctors and nurses.

Before you decide if you want to take part, it is important for you to know why the research is being carried out and what it will involve for you should you decide to join in. This short information sheet will give you a brief outline of the study, and explains why we need your help, and what we will ask you to do.

The Full Information Sheet that accompanies this one is more detailed and answers lots of questions about the whole study. It would be helpful for you to read it too. **You can call us anonymously if you have any further questions about taking part.**

Thank you for your time and the interest you have shown in our research.

Centre for Health Services Research,
University of Newcastle upon Tyne,
Newcastle upon Tyne NE2 4AA

Who is doing this study?	The LIFELAX research team is based in the University of Newcastle. We work with GPs across England and Scotland.
Why are you doing the study?	Constipation is a common and often bothersome problem for older adults. There are different ways of treating it. We are trying to find out the best way of doing this.
How are you going to do the study?	We are trying three different approaches. One uses laxative treatment, two look at changing your diet and lifestyle.
Why ask me to help in the study?	Your GP believes our research to be worthwhile and is supporting us. According to your medical notes, you have been prescribed laxatives often enough to take part in the study.
Do I have to take part in the study?	No. It is voluntary. If you do agree to join then change your mind you can leave at any time. We will need you to sign a consent form to say you are happy to join, but even then you can drop out.
What will I be asked to do in the study?	A member of the research team will contact you and answer any questions you might have. You will be asked to sign a consent form. A convenient time will be arranged with you for you to talk to a member of the research team on the telephone They will ask you some questions about your constipation. We ask everyone to fill in a daily diary about your bowel habits to monitor any changes during the study. We also ask you to fill in 4 postal questionnaires during the 12 months of the study. Some people may be asked about what it was like to take part in the study or get a telephone call to ask about the diet and lifestyle advice they were given. Just like before, this is voluntary and you don't need to take part.
Can I choose my treatment?	The treatment your surgery is asked to provide in the study was randomly chosen. This makes the study fair and equal. However, if you do not wish to continue in the study because you are not happy with the group your surgery is in, you should tell your doctor. They will then treat your constipation in whatever way you and your doctor think is best for you.
Do I need to have any medical tests or examinations?	No, not as part of our study.
Will you need to see my medical records?	Yes. This is because we need to see just how often you have been to see your GP during the study and what prescriptions you have had. This helps us to work out the cost of treating constipation.
Will my records, diary and questionnaire answers stay private?	Yes. We have to make every bit of information anonymous. Nothing you say can be traced directly back to you.
Has anyone checked to see whether this study is safe?	Yes. We have had it checked out by and approved by a Research Ethics Committee. It is sponsored by the NHS. We are not using any new or untried drugs. We have very strict rules to follow to make sure everything we do in the study is safe as it possibly can be.
I want to know more. What should I do?	The accompanying Full Patient Information Leaflet does tell you more about the whole study. If you can't find an answer to any of your questions in it, then please telephone Chris Speed.

LIFELAX brief patient information sheet – version 5 260506

LIFELAX full PIS, version 6 (24 July 2006)

ISRCTN7388134

UNIVERSITY OF
NEWCASTLE UPON TYNE

lifelax

A study about different ways of treating constipation in older people

Diet and lifestyle versus laxatives in the management of chronic constipation in older people.

We would like to invite you to take part in our research study. This study looks at the way that constipation in older people is treated by nurses and doctors.

Before you decide if you want to take part, it is important for you to know why the research is being carried out and what it will involve for you should you decide to join in please take time to read this sheet carefully - it answers many of the questions you may have. If you wish, you can show the leaflet to your family or friends and discuss it with them. If there is anything at all you are not clear about, or if you would like any more information, please ask one of the research team - our contact details can be found at the end of this sheet.

Please take your time to decide whether or not you wish to join this study - you don't need to make up your mind 'on the spot'.

Thank you for taking the time to consider the study.

Who is doing this study?
We are a team of researchers based at the Centre for Health Services Research at the University of Newcastle upon Tyne. This study is funded by the National Health Service. We will be working with GPs across England and Scotland.

Why is this study being done?
Constipation is a common and often bothersome problem in adults in the United Kingdom, particularly amongst those aged 50 and over. There are different ways in which doctors can treat it. Constipation can be treated by prescribing laxatives. It can also be treated by altering diet and lifestyle.

What do you want to find out?
We are carrying out the study because we need to know the best way to manage constipation in older people. To do this we need to compare the different types of treatment to see which one is best.

How is this study being done?
- **First –** we have recruited practices to the study (because you have this information sheet your surgery is taking part). Your practice will have been randomly selected to be in one of three groups. We will tell you more about these groups later in this leaflet.
- **Second –** we have helped practices to identify people, like yourself who can take part in our study.
- **Third –** doctors are inviting eligible patients to take part.

How and why have I been picked?
You have been chosen to take part because, according to your medical records, you have experienced constipation often enough and are in the correct age group for the study.
We need about 1500 people with constipation, both men and women, aged 50 and over and will be selecting patients from a number of general practices in England and Scotland

What are the benefits to me for taking part?
We hope that all the treatments on offer in the study will be of benefit to patients. However, there is no guarantee that an individual patient will get an immediate, direct benefit. We do hope that in the longer term our research will allow us to treat chronic constipation in a better way.

Do I have to take part?
No, it is entirely up to you whether you take part. We would like you to take your time, to read this information sheet and to think about the study. We would very much like you to help us, but if you decide not to take part, the care that you get from your GP's surgery will not be affected by your decision and no one will put pressure on you to take part. If you decide that you don't want to be part of the study you do not need to give us a reason.

Can I say 'Yes' now, and change my mind later?
Yes, you can. Even if you say 'yes' now you can leave the study at any time. You are not committing yourself to the study forever, and if you decide to leave you will not be asked for a reason.

What are the three groups you mentioned before?
As we said before, your practice will have been randomly selected to be in one of three groups. The three groups are:-

1) Your doctor will prescribe laxatives for your constipation.
2) Your surgery will give you standard, non-personalised dietary and lifestyle advice to help with your constipation.
3) Your surgery will give you personalised dietary and lifestyle advice, and you will be given ongoing help and advice to help with your constipation.

Can I or my surgery choose the group we are in?

No, it is not possible for you or your doctor to choose the group that you go into. This is because we have to make it as fair as possible for all practices and patients. Because none of the doctors can choose their favourite group there is an equal chance for all practices to go into each group. The group that a surgery is in is decided randomly (like the Lotto). Because there are three groups the surgery has an equal chance of one in three (33%) of being in a group. If you do not wish to be included in the study, you should tell your doctor. He or she will then treat your constipation in whatever way you and the doctor think is best for you.

Will there be any lifestyle restrictions for me?

There will not be any lifestyle restrictions as such for anyone taking part in the study. If you happen to be chosen for the Diet and Lifestyle group you will be offered advice on your lifestyle but whether you take it is entirely up to you. As with any treatment, please feel free to discuss any aspects of it with your doctor at any time.

What about any side effects from the treatment?

Because we are not trying out any new laxatives in the study, your doctor will be able to tell you of any known side effects for any of the laxatives they may prescribe. However, like any medicines, laxatives can have unwanted side-effects in some patients such as abdominal discomfort, bloating, flatulence etc. The likelihood and nature of these side-effects varies with the type of laxative but in general they are mild to moderate in intensity.

In the diet and lifestyle groups, you may notice a slight change in your bowel habits in the short term as it takes a while for any changes you make to take effect. Again, if you have any concerns about any aspect of your treatment or constipation you can talk to your doctor.

Is there another part to the study that I should know about?

We will be asking some people to talk to us about their experiences of their time in the study. If we ask you to be interviewed for that part of the study, we will ask you to sign a consent form to say that you agree to be interviewed. Again, this does not tie you down. You will still be free to change your mind at any time and leave this part or the whole study.

If I'm picked for the interviews, what will they be like?

The meeting will take place wherever feels most comfortable to you (e.g. at home or in your GP's surgery.. If you have to travel from your home for the interview, we will pay your travel expenses. The interview will take about an hour and will be conducted by an experienced researcher. It will be taped so that the researcher can talk with you without having to make too many notes. This allows the interview to flow like a conversation and to be quite informal. Anything you say at any stage or any information you give us will be strictly in confidence. You can ask to have the tape turned off at any stage during the interview and you won't have to give a reason. Only people in the research team will ever hear the tape.

What will happen next if I decide to take part in the study?

If you would like to join the study, you will need to send the research team your contact details using the enclosed form and envelope. A member of the research team will contact you and answer any questions that you might have about the study. They will send you a copy of a consent form to sign. When you have signed and returned it to the study team they will arrange a convenient time to

call you on the telephone to ask you some questions about your general bowel health, constipation and medication. The research team will also tell you about your special study diary and how to complete it We will ask everyone taking part in the research to fill in a diary to help us see which treatments are best.

After you have returned your consent form to the research team they will send a copy back to you along with a postal questionnaire. A copy of your consent form will be sent to your GP. We will also let your surgery know you are taking part in the study and need an appointment so your study treatment can begin. As we explained earlier, the treatment you receive at this appointment depends on the group your surgery is in.

Some people who were given diet and lifestyle advice will get a telephone call to ask about the diet and lifestyle advice they were given.

About three months after you join the study we will send you a questionnaire through the post. All we ask is that you would fill in the questionnaire and send it back to us. We will provide you with a stamped addressed envelope. We will ask you to fill in another questionnaire after six months and again after twelve months. Some patients will also receive a telephone interview to help in our economic evaluation in the study. You will be asked some simple questions about any costs you have had in connection with your constipation.

If when you start your study treatment, you decide that you don't want to take part in the research please tell the practice staff. They will let the study team know and we will destroy all of your study documents and paperwork including your consent form. No one will know what you said. Remember you don't need to give a reason why you don't want to take part.

Will you need to see my medical records?

In order to get all of the information about your constipation that we need, we will need to look at your notes at the end of the study. Again, all of this information will be kept private.

Will I get paid for taking part?

No, we are not paying anyone to take part in the study. Your doctors and nurses do not get paid for including you in this study. If you have to travel from your home for an interview at a later stage in the study, we will pay your travel expenses.

Has anyone checked out this study to see if it is all right?

When we applied to the NHS for money to do this research, our plans for the study were examined by other researchers to confirm that they are scientifically sound. The Multi-Centre Research Ethics Committee has reviewed the study. This committee is responsible for ensuring that all medical research going on in the area is ethical and fair to study participants like you.

I have private health insurance. Do I need to tell my insurer if I decide to take part in the study?

If you decide to take part in the study, it is most unlikely that it will affect any private health insurance that you may have. However, you should let your insurer know that you are taking part in the study.

Will anyone else know I am in this study?

Local GPs know that this study is going on. We have written to all practices to tell them of our work. Only your own GP's surgery will know that you personally are in the study. One issue that we need to draw to your attention at this stage is that the people who wrote some of the questions we will use in our research (Jansen Pharmaceuticals Ltd.) ask for our

data to be sent to them so that they can further refine their questionnaire. At this stage we make sure that no information that can identify any patient or doctor is sent. These data will be made completely anonymous and no individual or practice will be identifiable at any time.

Will what I tell you be kept private?

Other than staff in your practice, only the research team who will be running the study, and collecting and analysing information from study participants, will know who is in this study. We are all bound by a written code of confidentiality. This means that we must take great care to prevent anyone from outside the research team seeing any personal information about you, and we must not tell anyone else what you say. So all the information the research team has about you (e.g. from the interviews, questionnaires and examining your medical records) will be kept private. Any information about you which leaves the surgery will have your name removed so that you cannot be recognised from it. On your questionnaire, you are only identified by a number. Only people in our office will know who the questionnaire came from. Anything you tell us will be kept secret. We will not tell anyone what you have said unless you ask us to. If you decide to withdraw from the study at any point all data and personal information collected will be destroyed.

What will happen to the results from the study?

At the end of the study, in 2006, the research team will write a report of the results for the NHS. After that, we will write articles about the findings for publication in the magazines that other health workers and carers read. In all the reports that we write, we will take great care that no individual patient can be identified. All the information the research team have about you will be kept private. If you would like a copy of the findings of the study, we will send them to you.

How can I get more information about the study?

Please feel free to contact a member of the research team if you would like some more information about the study, or if you have any questions you want answered. Our phone numbers are shown on the next page. You may contact us right through the study. It's best to call during office hours (9.00-12.30, 1.30-5.00) but we do have an answer machine switched on when we are out of the office. If you prefer to write to us, our addresses are also shown on the next page.

The LIFELAX Research Team

The LIFELAX team (from left to right)

Dr Elaine McColl (Study Coordinator)
Mr Chris Speed (Trial Manager)
Mr Ben Heaven (Researcher doing interviews)
Ms Erika Tandy (Project Secretary)

LIFELAX office address

Centre for Health Services Research
University of Newcastle upon Tyne
21 Claremont Place
Newcastle upon Tyne
NE2 4AA

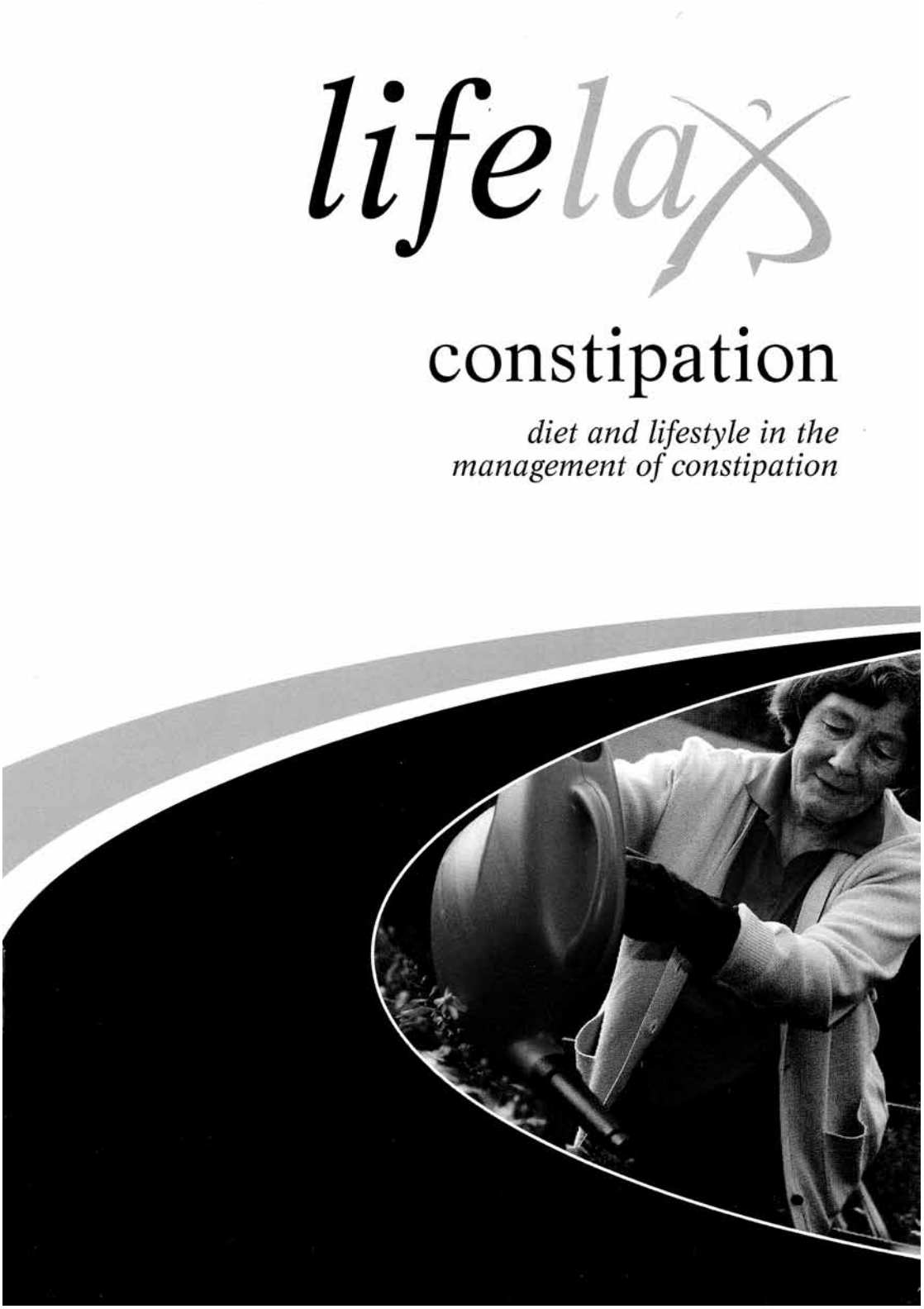
Appendix 3

Contents pages from the intervention manuals and patient information leaflets

Standardised intervention arm
Contents of the training manual

CONTENTS

Standardised PIL



This leaflet is to tell you about:

Fibre

Fruit and Vegetables

Fluid

Activity

Toileting

Medication/Laxatives

And how these may help relieve your constipation.

lifelax

diet and lifestyle in the management of constipation

constipation

Nearly everyone becomes constipated at some point. This information is to tell you a bit more about constipation and what you can do to help relieve it.

what is a normal bowel habit?

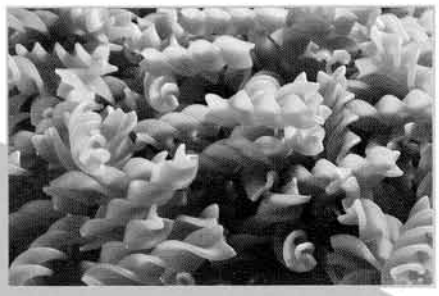
Individuals vary in how often they open their bowels – it ranges between three times a day and three times a week. So don't be anxious if you don't pass a daily stool. A stool should be solid and easy to pass.

diet and lifestyle in the management of constipation *lifelax*

what is constipation?

Constipation is a symptom not a disease; it may result in one or more of the following:

- Stools become hard, difficult or painful to pass.
- Your frequency of toilet trips decreases.
- You get cramp like pains in your lower abdomen.



what causes constipation?

Diet – not eating enough fibre (fruit, vegetables, cereals).

Not drinking enough – ensure you have a variety of fluids throughout the day rather than just strong tea or coffee.

Bad bowel habits – ignoring the urge to go to the toilet may result in the stool drying out, becoming hard and more difficult to pass.

lifelax diet and lifestyle in the management of constipation

Medicines – some medication can cause constipation. Speak with your doctor if you suspect this.

Regular use of stimulant laxatives – these can make the bowel 'lazy' and begins a vicious cycle.

medicines which may cause constipation:

- Antacids containing aluminium or magnesium.
- Some pain killers e.g. codeine.
- Iron tablets.
- Some anti-depressants.
- There are other medications which may cause constipation check with your doctor.

diet and lifestyle in the management of constipation *lifelax*

Your constipation can be made worse by:

- Dehydration.
- Inactivity.
- Emotional upset.
- Painful anal conditions e.g. piles.
- Poor toilet facilities.

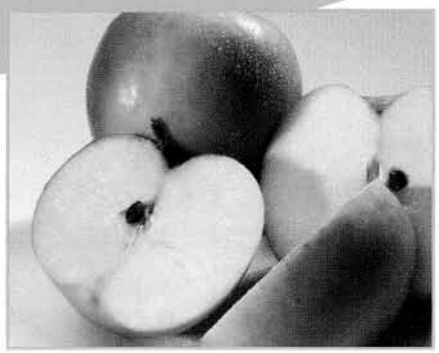
how can you ease your constipation?

Try some of these ideas before using laxatives:

- Eat **regularly**.
- Eat more **fibre**.
- **Fruit**: dried, fresh, tinned (in own juice) and fruit juice.
- **Vegetables**: fresh, frozen and tinned.
- If you have problems chewing try chopping or pureeing fruit and vegetables.

lifelax diet and lifestyle in the management of constipation

- **Cereals**: Choose a brand containing wheat, bran or oats e.g. Bran Flakes, Fruit and Fibre, Weetabix, Porridge, All Bran, instead of Cornflakes or sugar coated cereals.
- If cereals are difficult to chew, try soaking overnight in milk.
- **Wholemeal bread.**
- **Drink lots: 8 to 10 cups** per day of water/ juice/ soft drink but avoid too much strong tea, coffee or alcohol.
- **Exercise regularly** – keeping active helps your bowels to keep active, even if you have a disability.
- **Routine** – go to the toilet as part of a routine e.g. as soon as you are up or after breakfast.



diet and lifestyle in the management of constipation *lifelax*


Goals
1
2
3
4
5
Shredded Wheat
100%
RYVITA
Dark Rye

Toileting – listen to your body when you feel like going to the toilet and take time going.

- Sit in a relaxed, comfortable position on the toilet.
- You may find it helpful to sit with your legs slightly apart and to lean forward.
- Most importantly, relax and take your time.

If you still have concerns about your constipation and it is not responding to simple treatments please see your doctor (especially if there is rectal bleeding or new symptoms like pain or distension).

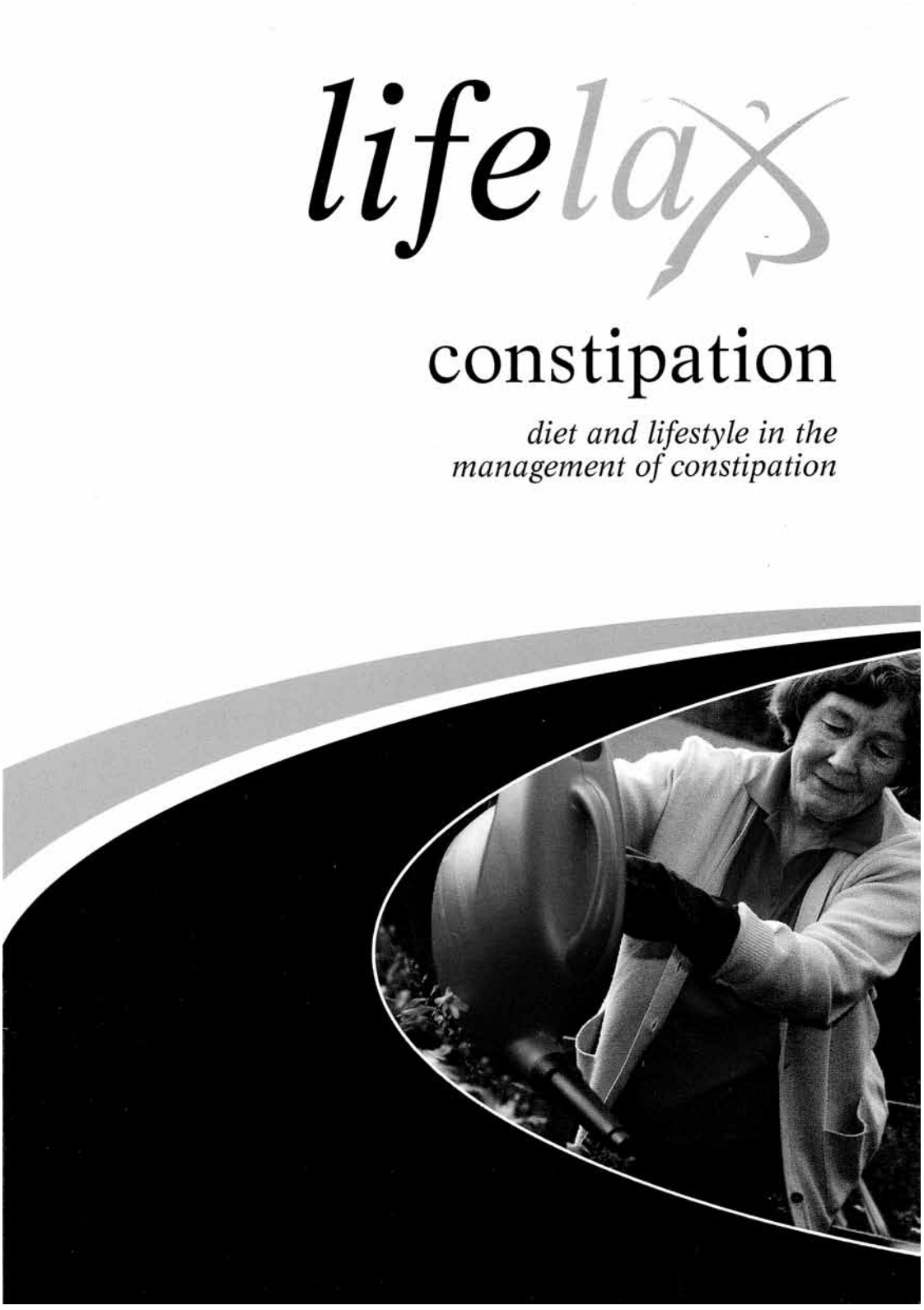
UNIVERSITY OF NEWCASTLE UPON TYNE

University of Newcastle School of Population & Health Sciences 21 Claremont Place Newcastle upon Tyne NE2 4AA

Personalised intervention arm
Contents of the training manual

diet and lifestyle in the management of constipation

Personalised PILs
Constipation



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lifelax diet and lifestyle in the management of constipation

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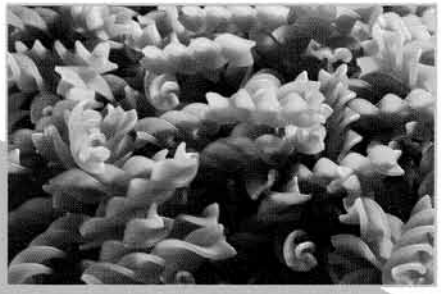

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lifelax diet and lifestyle in the management of constipation

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diet and lifestyle in the management of constipation *lifelax*

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lifelax diet and lifestyle in the management of constipation

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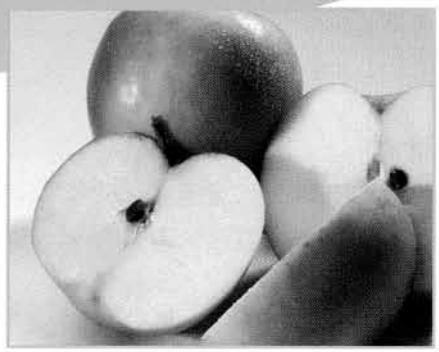

diet and lifestyle in the management of constipation *lifelax*

Toileting – listen to your body when you feel like going to the toilet and take time going.

- Sit in a relaxed, comfortable position on the toilet.
- You may find it helpful to sit with your legs slightly apart and to lean forward.
- Most importantly, relax and take your time.

If you still have concerns about your constipation and it is not responding to simple treatments please see your doctor (especially if there is rectal bleeding or new symptoms like pain or distension).

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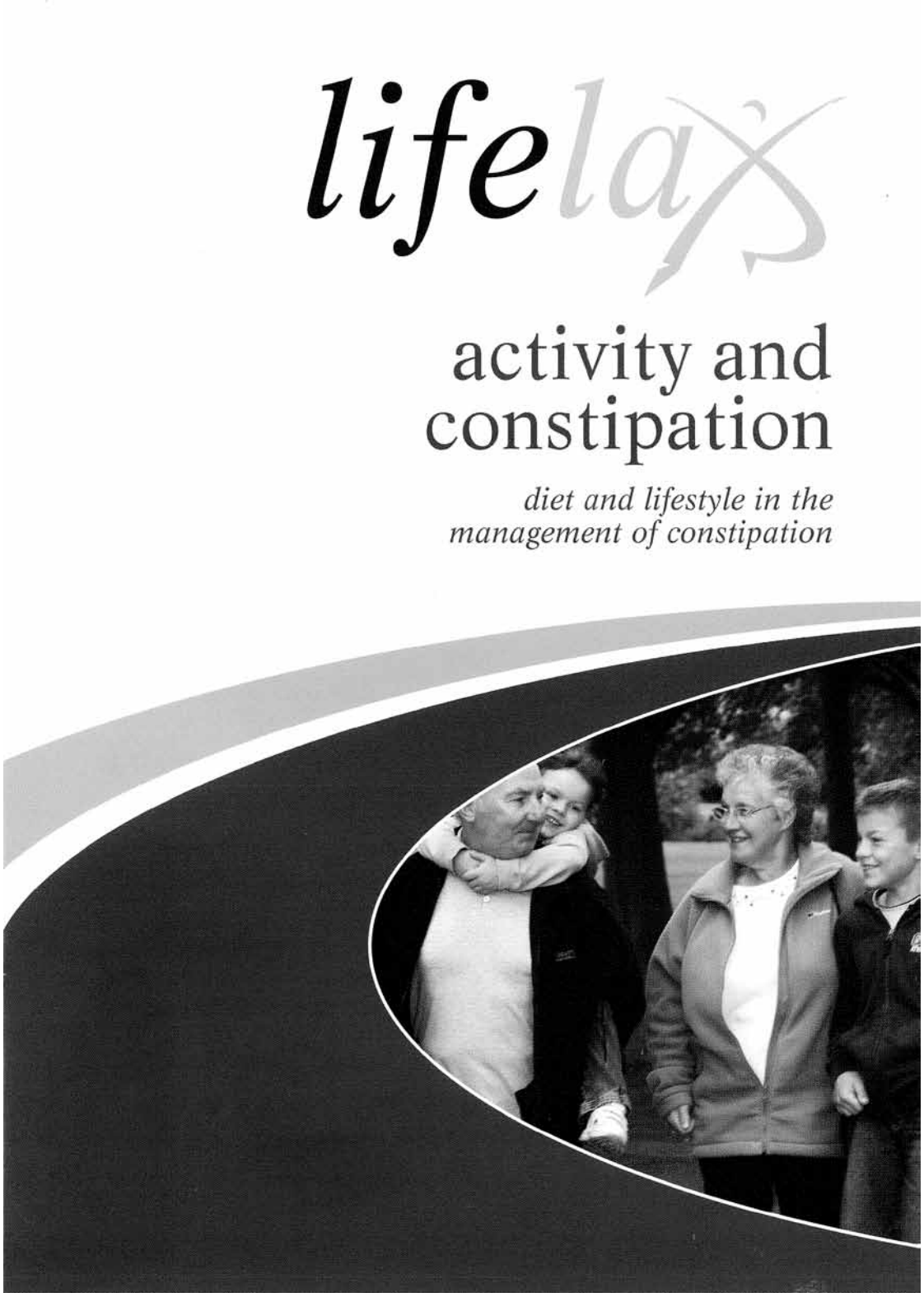
Activity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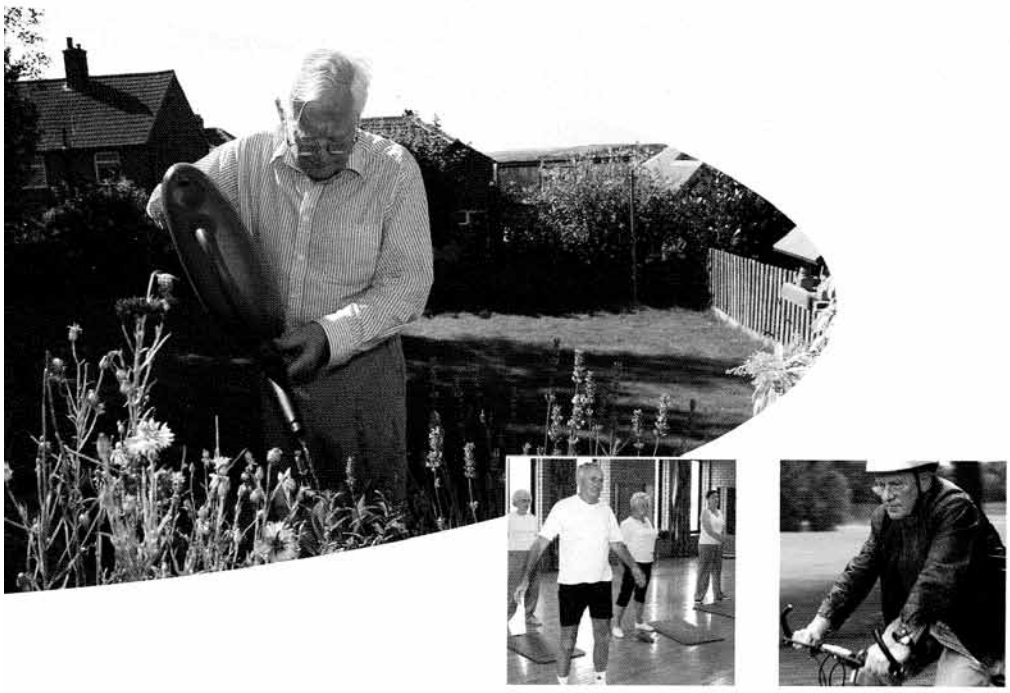
activity and constipation
diet and lifestyle in the management of constipation

why is being active important for you?

- Being active helps prevent constipation because it stimulates bowel movement.
- It can also have other health benefits such as managing back pain and lowering blood pressure.
- Being active can help you stay mentally and physically fit in old age.



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what sort of activity should you do?

- Any type of activity is suitable as long as you enjoy it.
- You may experience a few aches when starting exercise. This is normal. However persistent or severe pain should always be investigated by a doctor.
- You should attempt to do moderate exercise which means moving about enough to make you feel warm and slightly out of breath.

- This may be part of your usual routine such as walking to the shops, gardening or housework.
- It may be something you do as a hobby such as swimming or playing bowls.
- If you are not able to exercise, try being seated and doing stationary exercises.
- Remember do a warm up before exercising and then do some simple stretches after exercising.

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how much activity should you do?

- Try to gradually work up to doing 30 minutes of activity a day.
- You could do short bouts of activity e.g. 2 sessions of 15 minutes.
- Walking within 30 minutes after you have eaten can help constipation.

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how much exercise do YOU do?

Use the table below to fill in how often you exercise in a usual week.

	Never (0)	1 time a wk (1)	2-3 times a wk (2.5)	4-6 times a wk (5)	Once a day (7)	More than once a day (10)	Score
Vigorous exercise lasting 30 mins or more?							x 5
Moderate exercise lasting 30 mins or more?							x 3

Vigorous exercise makes you breathe harder or puff and pant, e.g. jogging, squash, vigorous swimming etc.

Moderate exercise does not make you breathe, puff or pant too hard, e.g. walking, gardening, bowling etc.

A score of 15 is equivalent to moderate daily activity (recommended amount of exercise).

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some exercise tips

- If you sit down a lot, get up whenever you can and walk around.
- If you can manage, take the stairs instead of the lift.
- Put more effort into physical activities you do.
- If you use the bus get off a stop earlier and walk the rest.
- If you can, walk or cycle short journeys instead of using the car/bus.
- Check out different activities.
- Try and push yourself a little further each time but don't overdo it!
- Exercising with a friend will help you keep up your routine and make it more fun for you.

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wake up with a stretch

Sit in bed and reach your arms to the ceiling while inhaling. Exhale when lowering.

Stand up straight and reach your right arm up to the ceiling and stretch. Do the same with your left.

Reach both arms to the ceiling, cross them over and intertwine your hands making sure your palms are facing each other. Stretch upwards.

Stand straight and lift your shoulders up to your ears, roll them backwards or forwards then drop them down. Repeat this five times.

Sit on the edge of your bed, lift your leg and start rotating your foot one way then the other for a few minutes. Repeat with the other leg then your hands.

From standing, lower yourself so you sit on your ankles with knees bent for 2-3 minutes.

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Remember you can help your constipation by:

- Being more active: remember to drink more.
- Drinking plenty of fluid: about 8-10 cups per day – try soft drinks and not too much strong tea or coffee.
- Eating more fibre rich foods such as wholegrain breads, cereals and porridge: remember to drink plenty.

- Eating more fruit and vegetables.
- Listening to your body: go to the toilet when it tells you to and leave enough time for toileting.

You may find you have some bloating and wind at first – but as your bowel becomes used to the extra fibre this will settle down.

If you have any existing medical condition or have any concerns about your health, please contact your GP prior to starting exercise.

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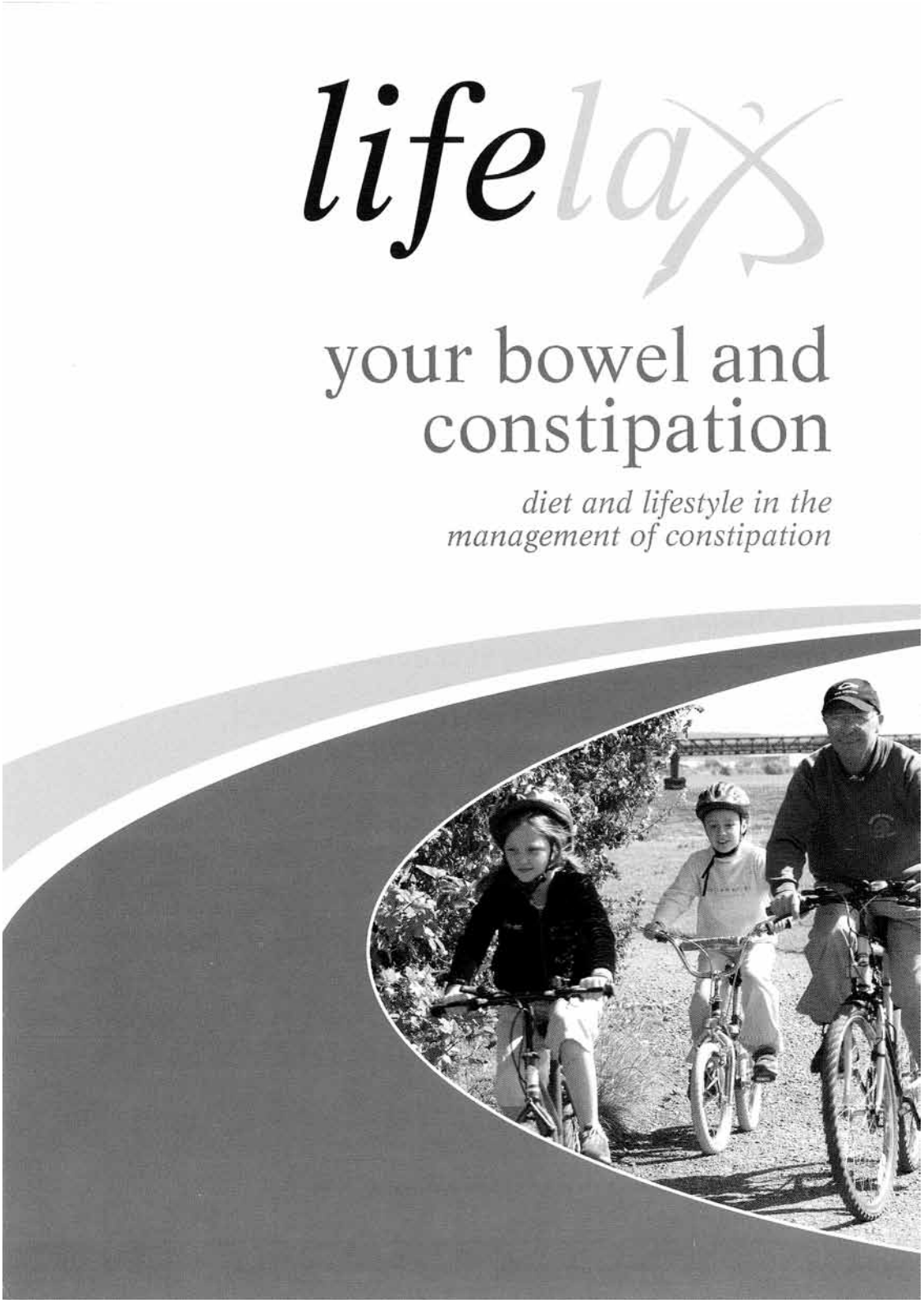
Bowel health



A **healthy bowel** is home to around 100, 000, 000, 000, 000 bacteria!

As we get older it is harder to maintain our **'friendly' bacteria**.

The **'friendly' bacteria** have an important role in maintaining the health of your bowel, such as:

- Producing acids to stimulate the movement of food through the digestive system.
- Breaking down food.
- Producing nutrients.

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Eating fibre gives the 'friendly' bacteria food to digest.

Some yoghurts and milky drinks contain 'friendly bacteria' to help restore the balance of bowel bacteria, improve your bowel health and function.

These yoghurts and drinks can be found in the chilled areas of the supermarket.

These are usually dairy products and may be unsuitable if you have a dairy intolerance, check with your GP.

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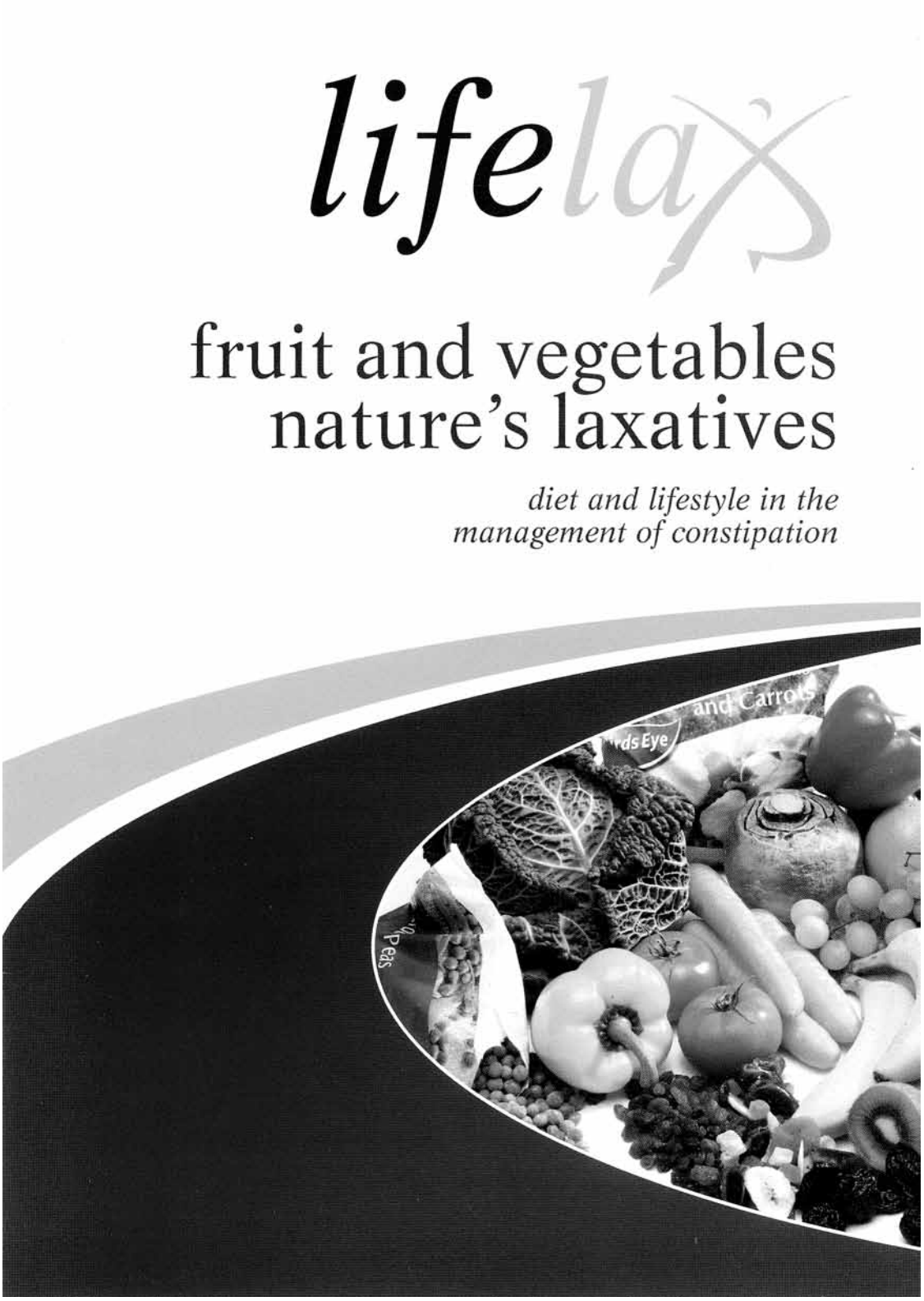
Fruit and vegetables



constipation

- Humans have been plagued by constipation for centuries.
- For over 2000 years foods have played an important role in treating a range of symptoms and diseases.
- Some foods known to help relieve the symptoms of constipation include fruit, vegetables, wholegrain products such as bread, cereals and also fluid.
- This booklet will concentrate on fruit and vegetables which are high in fibre.

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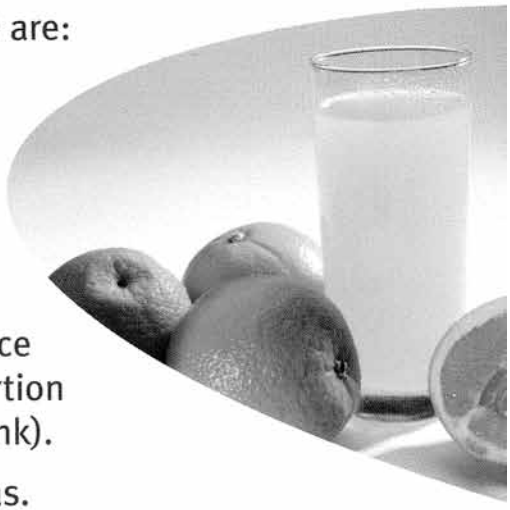
are you having five portions of fruit and vegetables?

- Aim to eat at least 5-portions of a variety of fruit and vegetables a day.
- Fresh, frozen, canned, 100% juice and dried fruit all count towards 5-a day.
- Fresh, frozen, canned and 100% vegetable juice all contribute to 5-a day.
- A portion is equivalent to 80g (3oz).

Some examples of portion sizes are:

- 2 florets of cauliflower.
- 1 medium pear.
- 1 medium banana.
- 1 medium apple.
- 1 medium glass of orange juice (juice can only count as 1 portion a day, however much you drink).
- 2 heaped tablespoons of peas.



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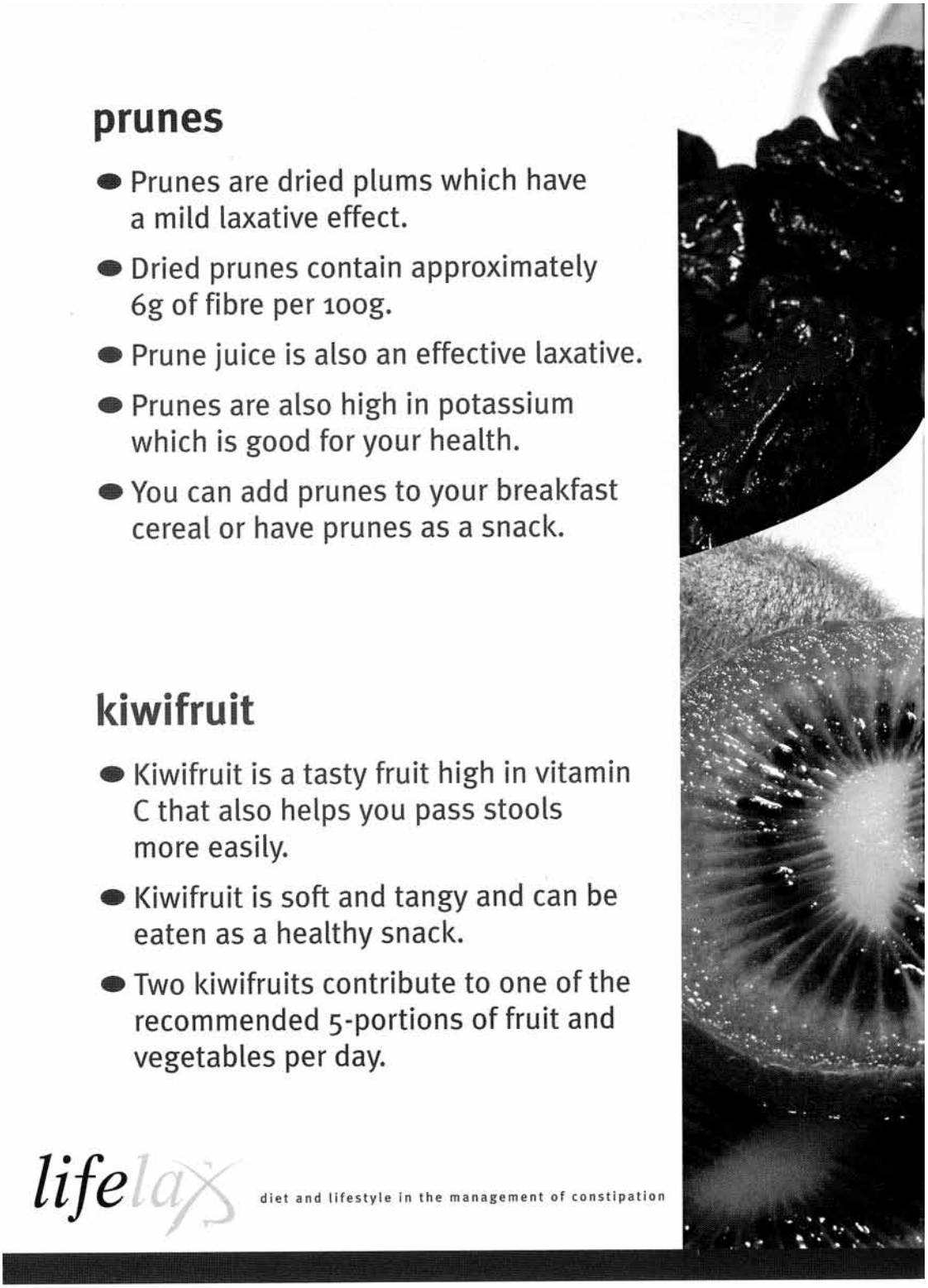

milk jelly and fruit

¼ pack of jelly
¼ pint milk
fruit (tinned in own juice or fresh), chopped.

method,

1 Melt jelly with a little water,
2 Make up to ¼ pint with milk,
3 Pour into serving dish and add fruit,
4 Refrigerate until set.

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vegetable risotto *(serves 3)*

1 onion, chopped

1 tablespoon oil

1½ mugs wholegrain (or brown) rice, easy-cook or risotto rice

1 carrot

1½ leeks, sliced

8 mushrooms

1 tin tomatoes

grated cheddar cheese for topping.

method,

1 in a large pan fry the onions in oil until soft,

2 add rice and cook for 2 mins,

3 add tomatoes and all the chopped vegetables to the rice and pour over 1 pint boiling water,

4 boil the mixture until the water is absorbed

5 add 1 more pint of water, stir until bubbling. Reduce heat to low and cover pan with lid

6 cook for 25-30 mins, until rice is tender, stirring occasionally. Season and sprinkle with the grated cheese.

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compote of dried fruits *(serves 2-3)*

1 (250g) packet dried fruit salad (ready to eat)

5fl oz (150ml) orange juice

1 teaspoon honey (optional)

method,

1. place all ingredients in a pan, bring to the boil and simmer for 10 mins,
2. cover and leave to cool.

Lovely eaten for breakfast topped with plain yogurt or as an accompaniment to high fibre cereals e.g. Weetabix or Bran Flakes.

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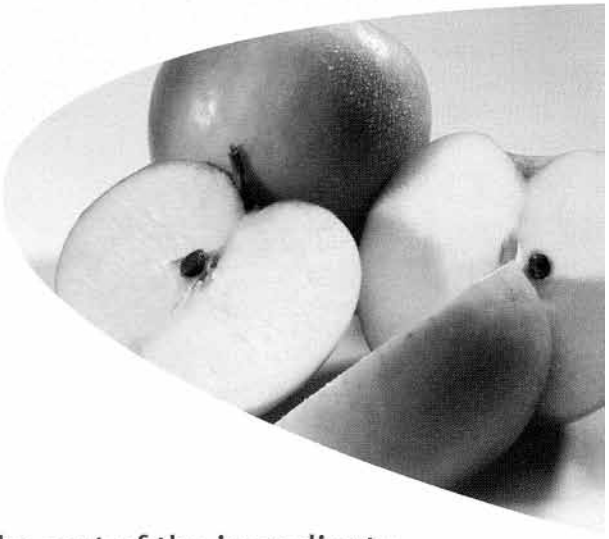
apple and cheese toast

1 thick slice of bread (granary or wholemeal)
½ eating apple, grated
2oz (50g) cheese, grated
pinch of mustard powder (optional)



method,

1 toast bread,

2 meanwhile, combine the rest of the ingredients in a bowl,

3 place the topping onto the toast (use a fork to press it down),

4 grill until cheese is melting and golden brown.

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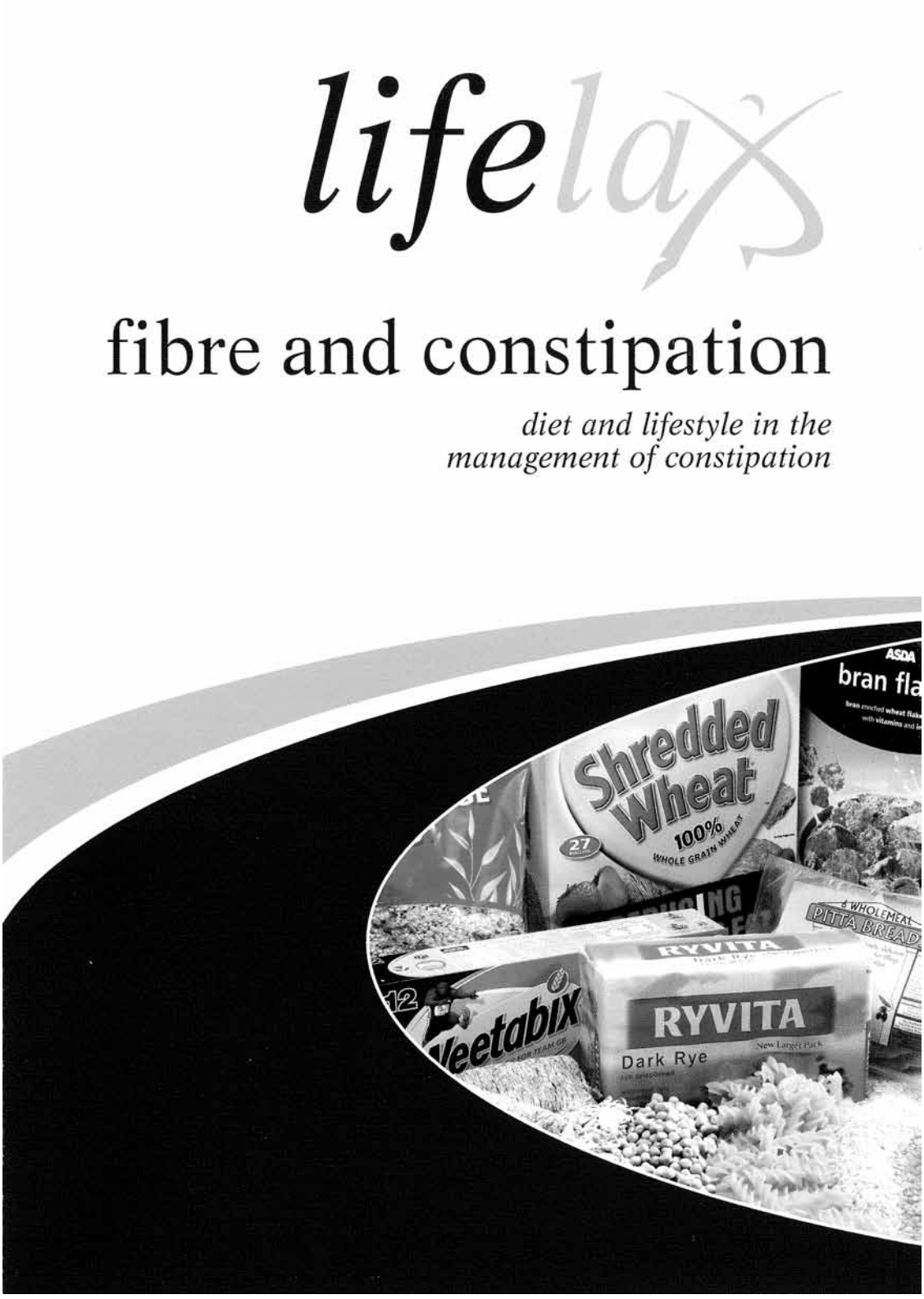
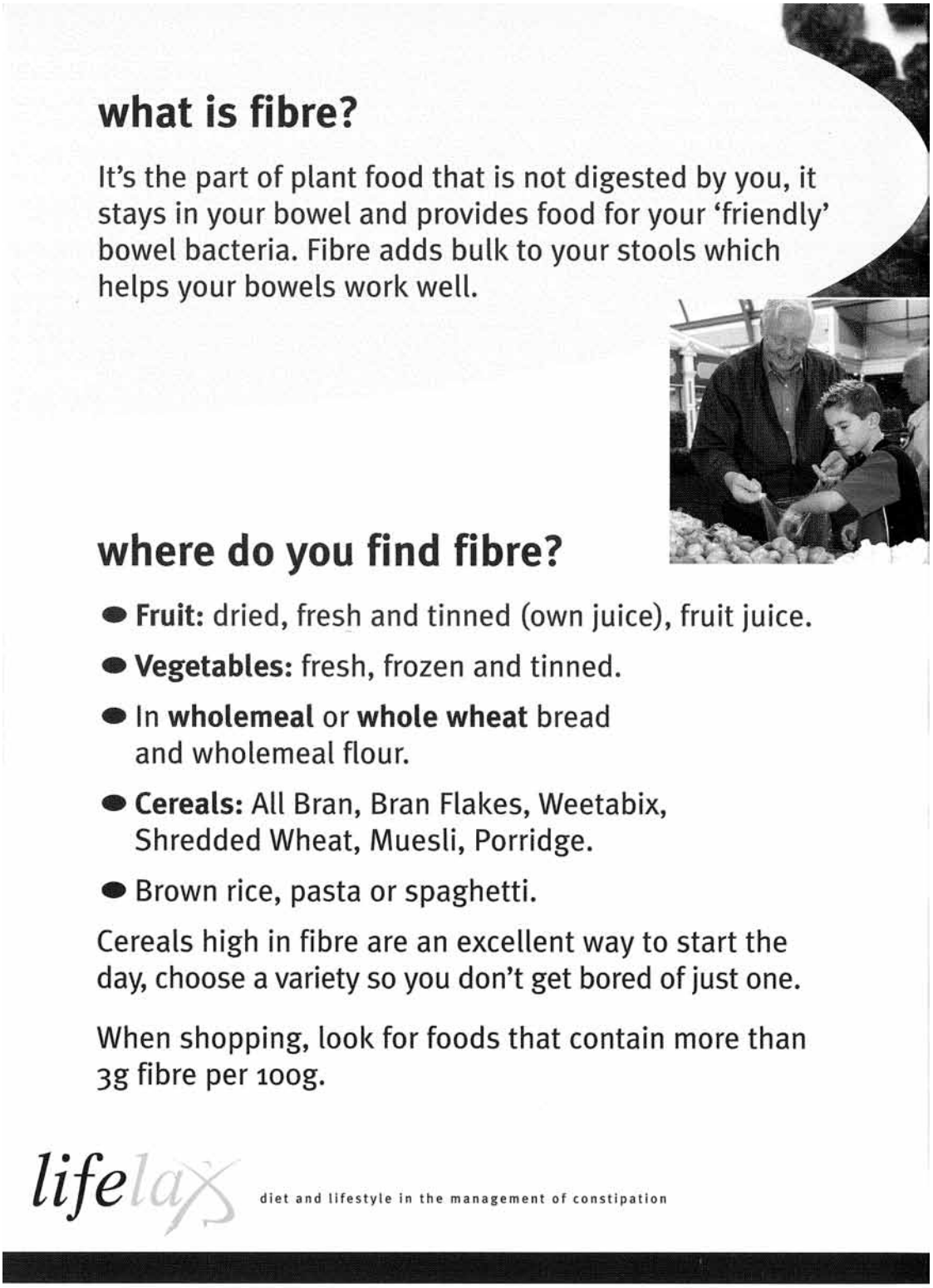
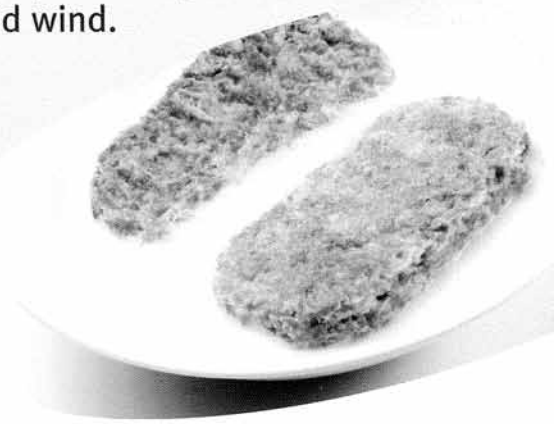
Fibre and constipation





what are the benefits of fibre?

- Fibre **prevents** constipation and maintains a healthy bowel.
- Can encourage the growth of friendly bacteria in the bowel.
- Fibre helps with **weight loss**: fibre is filling, but not fattening.
- Fibre needs fluid to work effectively.
- Increase your fibre gradually as it may initially cause bloating and wind.



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Remember you can help your constipation by:

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Fibre

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fibre counter

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how much fibre do you eat?

Use the fibre counter to add up how much fibre you eat.

1 About how many **pieces or slices per day** do you eat of the following types of bread, rolls, or chapatis? (Choose one answer on each line)

Breads & Rolls	0	Less than 1 a day	1-2 /day	3-4 /day	5+
White bread or rolls	0	1	4	9	13

Breads & Rolls	0	Less than 1 a day	1-2 /day	3-4 /day	5+
Brown or granary bread or rolls	0	2	7	15	22

Breads & Rolls	0	Less than 1 a day	1-2 /day	3-4 /day	5+
Wholemeal bread or rolls	0	3	8	18	26

Total Bread	

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2 About how many **servings per week** do you eat of the following types of breakfast cereal or porridge? (Choose one answer on each line)

Breakfast Cereals	0	Less than 1 a week	1-2 /week	3-5 /week	6+
Sugared type: Frosties, Coco Pops, Ricicles, Sugar Puffs **Rice or corn type:** Corn Flakes, Rice Crispies, Special K	0	0	0	1	2

Breakfast Cereals	0	Less than 1 a week	1-2 /week	3-5 /week	6+
Porridge or Ready Brek **Wheat type:** Shredded Wheat, Start, Weetabix, Fruit'n Fibre, Puffed Wheat **Muesli type:** Alpen, Jordan's	0	1	2	5	7

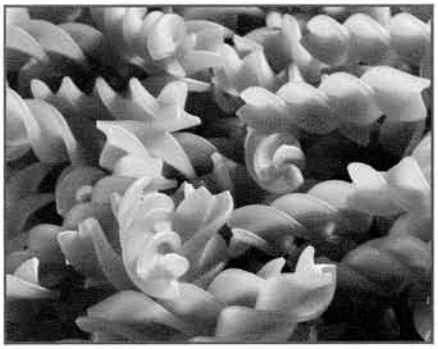
Breakfast Cereals	0	Less than 1 a week	1-2 /week	3-5 /week	6+
Bran type: All-Bran, Bran Flakes, Country Bran	0	2	5	12	18

Total Cereal	

3 About how many **servings per week** do you eat of the following foods? (Choose one answer on each line)

Vegetable foods	0	Less than 1 a week	1-2 / week	3-5 / week	6-7 / week	8-11 / week	12+
Pasta or rice	0	0	1	3	4	6	8

Vegetable foods	0	Less than 1 a week	1-2 / week	3-5 / week	6-7 / week	8-11 / week	12+
Potatoes	0	0	1	3	5	8	10



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Vegetable foods	0	Less than 1 a week	1-2 / week	3-5 / week	6-7 / week	8-11 / week	12+
Peas	1	1	3	8	12	16	24

Vegetable foods	0	Less than 1 a week	1-2 / week	3-5 / week	6-7 / week	8-11 / week	12+
Beans (baked, tinned, or dried) or lentils	1	1	4	10	15	20	30

Vegetable foods	0	Less than 1 a week	1-2 / week	3-5 / week	6-7 / week	8-11 / week	12+
Fruit (fresh, frozen, or canned)	0	0	1	3	5	8	10

Vegetable foods	0	Less than 1 a week	1-2 / week	3-5 / week	6-7 / week	8-11 / week	12+
Other vegetables (any type)	0	0	1	2	3	5	6

Total Vegetables	

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Add totals together: _____

		Less than 30	=	Low fibre intake		**Total**	
	Fibre Rating	30 to 40	=	Medium fibre intake			
		More than 40	=	High fibre intake			

Remember you can help your constipation by:

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- Drinking plenty of fluid: about 8-10 cups per day – try soft drinks and not too much strong tea or coffee.
- Eating more fibre rich foods such as wholegrain breads, cereals and porridge: remember to drink plenty.

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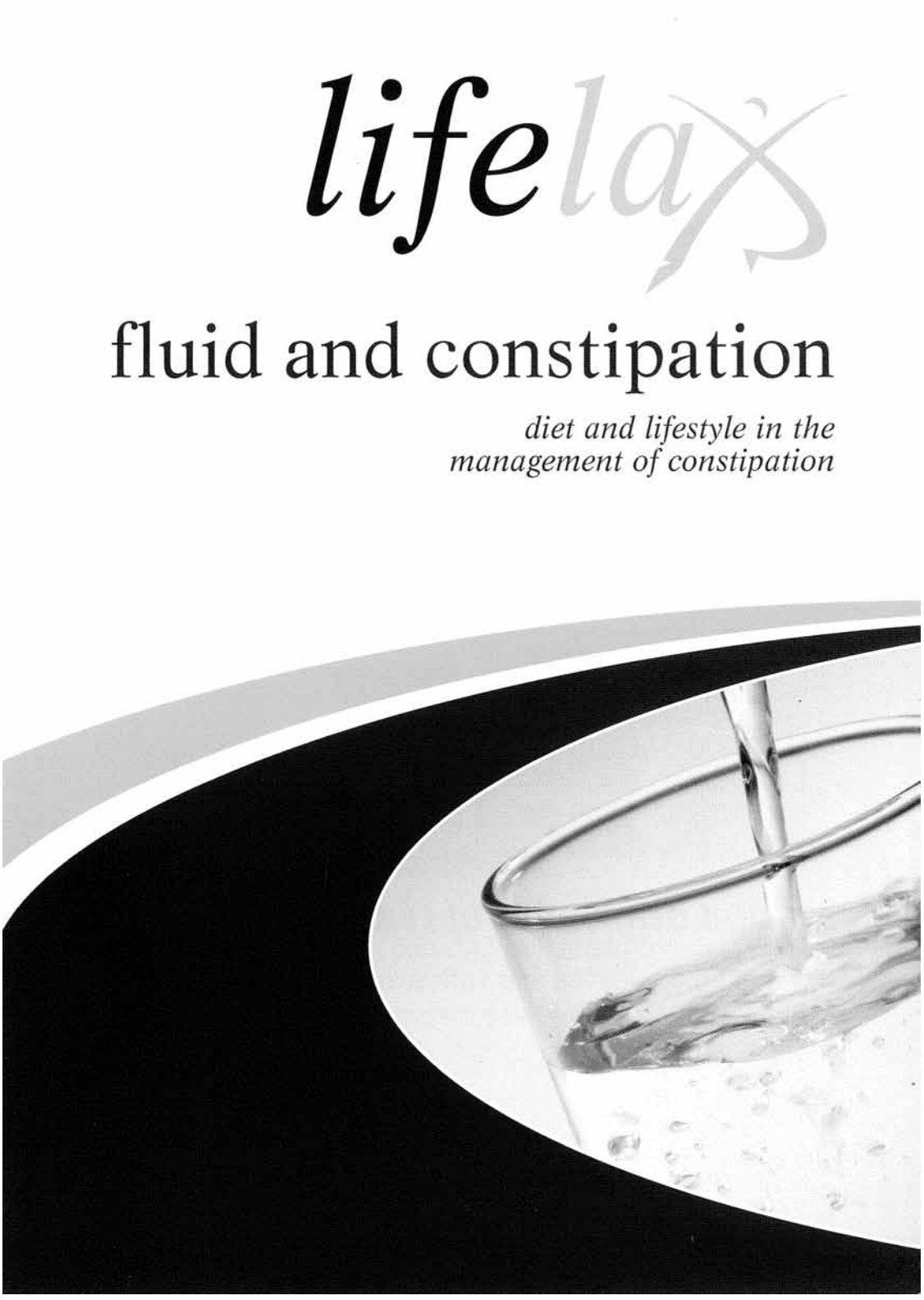
Fluids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why are fluids important for you?

Fluid is important:

- To prevent your body becoming dehydrated.
- To bulk up your stools so they are softer and easier to pass.
- To relieve constipation.

It is likely that you won't feel thirsty a lot of the time, especially if you are stressed or feeling ill, but try and continue having soft drinks.

Alcohol is dehydrating and may make constipation worse.

do you drink a lot of tea or coffee?

Try and limit your tea and coffee intake to no more than 6 cups a day because these may make constipation worse. Have a variety of other drinks instead.

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how much do you drink?

Use the fluid counter to add up how much you drink in a day.

Fruit/vegetable juices

Sugar free fizzy drinks/squashes

Water

Squashes/ fizzy drinks

Hot drinks e.g. tea/coffee/soup

Other e.g. smoothies

How many of these do you drink in a day?

Total =

Aim to drink 8-10 cups each day of a variety of fluids.

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when should you have extra drinks?

If you have increased your fibre intake remember fibre absorbs fluid so it's important you have plenty to drink.

Make sure you have enough fluid to drink in hot weather or if you have a fever. Coffee, tea and alcohol are dehydrating so remember to drink other fluids.

When you exercise remember to increase your fluid intake to replace water lost during sweating.

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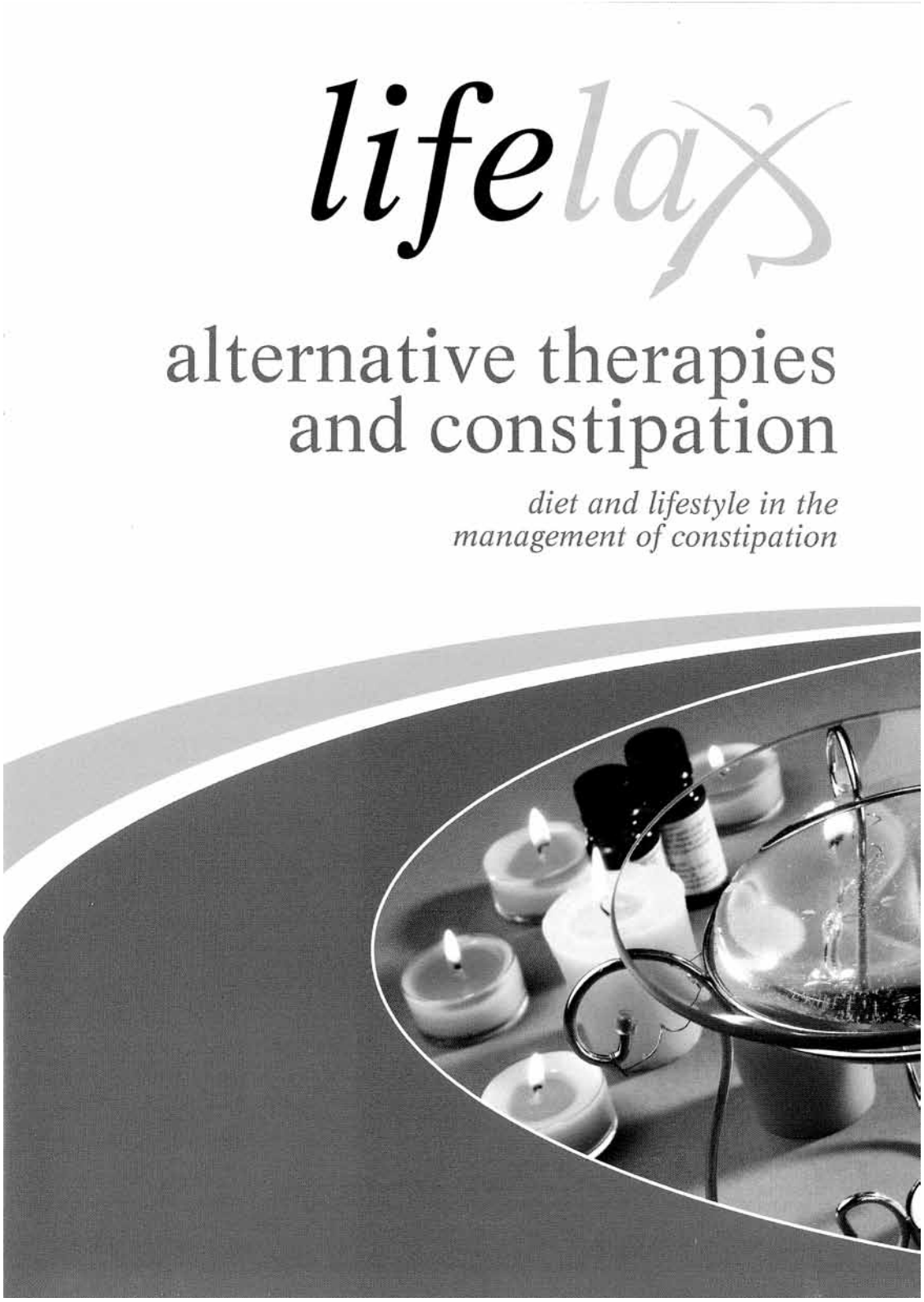
Alternative therapies



This booklet describes some ideas to help you relax which MAY help your constipation.

relaxation

- Try having a long leisurely soak in the bath. Soaking in body-temperature water is effective at helping you unwind. For an added benefit use aromatic oils.
- Pamper your body after bathing. Dusting powders, creams and lotions such as rose and lavender remoisturise the skin.
- Burning candles and using incense or aromatic oil-burners will help create the mood for relaxing. Sit quietly with eyes closed, mind switched off and breath in the beneficial aromas for 10 minutes.
- Meditation and gentle yoga stretches will quieten the mind and release body tension. Sit or lie down, close your eyes and focus on breathing in and out slowly.
- Listening to music may help you relax because it is a good mood lifter and antidote for anxiety.
- Make sure you have some quiet time to yourself during the day where you can go for a walk or read a book.
- Massages are a great way to help your body and mind let go and unwind.

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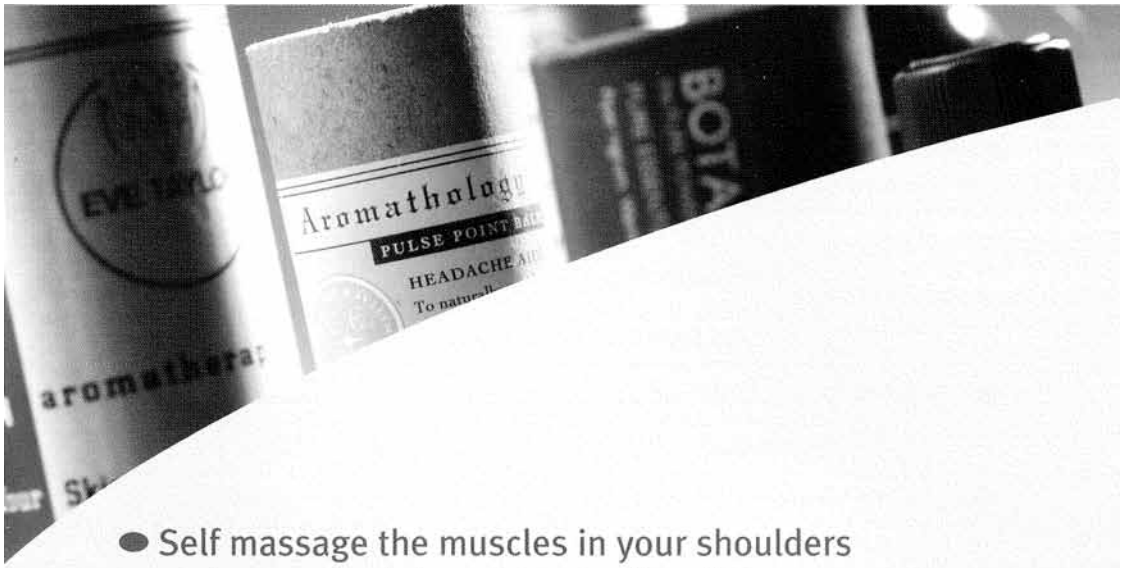

- Self massage the muscles in your shoulders and upper back by using your hands in a squeezing movement. Move your hand firmly along the top of your shoulder to the neck and then back. If you feel any tension spots apply circular pressure with your fingers. Repeat on the other shoulder.

what can an abdominal massage do for your constipation?

It may help in the elimination of waste products by:

- Encouraging the bowel to move.
- Assisting in the bowel opening.

It may also:

- Stabilise bowel patterns.
- Relieve wind.

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are there any other advantages of a massage?

- Reduces anxiety.
- Reduces psychological distress.
- There are no known side affects unlike certain laxatives.
- Can be used with other types of therapy.

- Pleasant, relaxing and safe technique.
- Easy to learn the technique.
- Once you are trained, it can be done by yourself.

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are massages suitable for everyone?

Before you proceed massage you should check with your GP or carer to see if you are suitable for an abdominal massage.

You should not receive a massage if you have:

- Bowel cancer.
- Hernia.
- Had recent surgery or scarring.
- Received radiotherapy to the abdomen in the last six weeks.
- Known or suspected abdominal obstruction.
- A large abdominal mass (unless permission has been given by medical staff).

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who should perform the massage?

Abdominal massages should be administered by staff fully trained in the technique.

The trained staff member may teach you how to self-massage.

other massage tips

- The massage should be performed every day.
- The best time for the massage to be performed is early morning when there is more movement in the bowel, but it can be effective at other times too.
- A massage lotion can be used to make massage strokes more comfortable.
- There are a variety of lotions that can be used such as a non-perfumed white lotion which has essential oils added to it e.g. Black Pepper, Roman Chamomile.

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acupuncture

- There is some evidence this treatment can help constipation.
- See a qualified Acupuncturist.

reflexology

- Massaging the reflexes present in your feet can benefit the whole body.
- Rest your foot on the knee of your opposite leg and using firm circular motions massage the sole.
- Use a firm thumb pressure to ease painful areas of tension.
- Repeat with the other foot.

See a qualified reflexologist for specific treatments.

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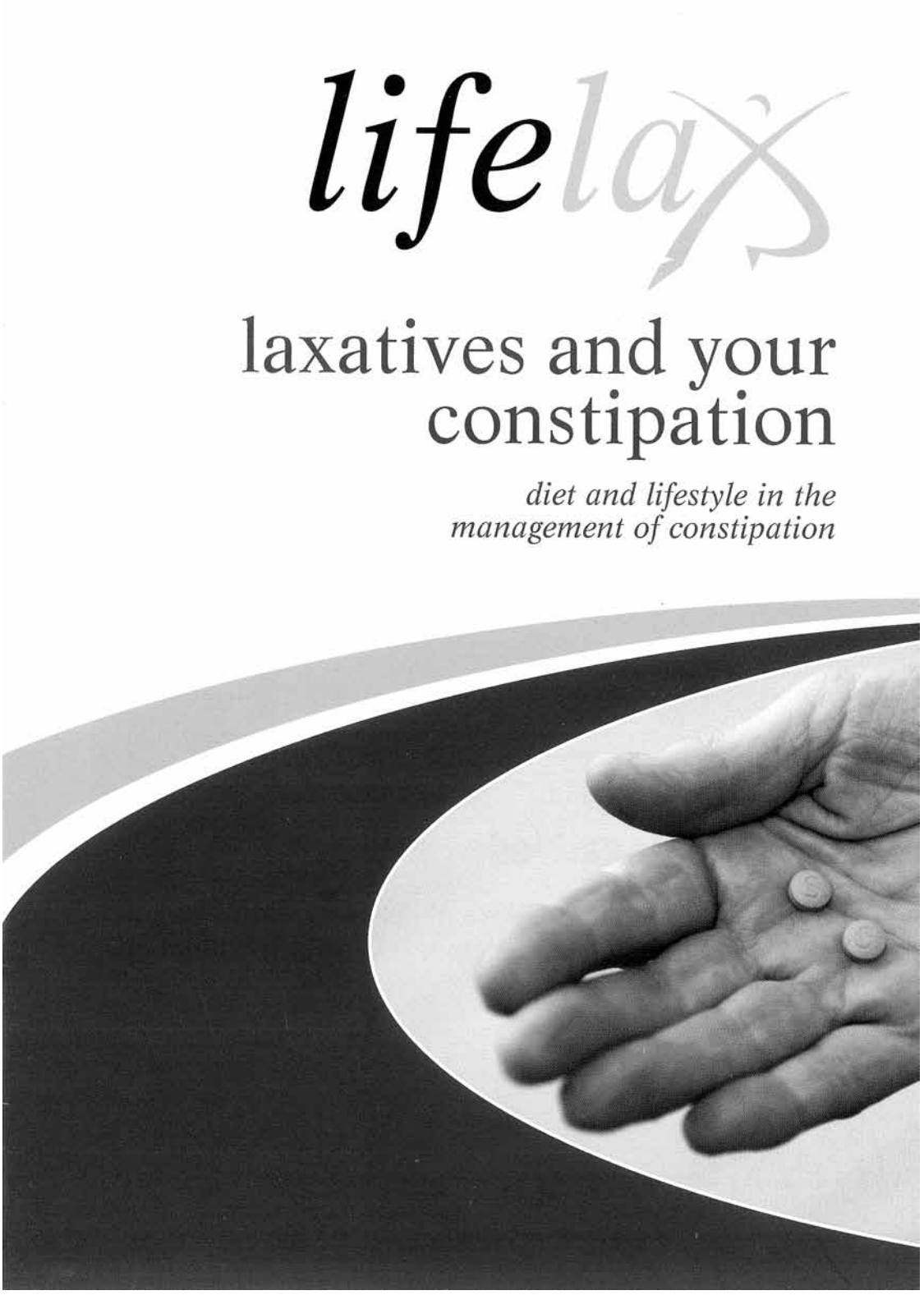
Laxatives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laxatives and your constipation
diet and lifestyle in the management of constipation

what are laxatives

Laxatives are medicines taken to encourage bowel movements to relieve constipation.

types of laxatives

There are a number of types of laxatives which work by different mechanisms to help relieve your constipation.

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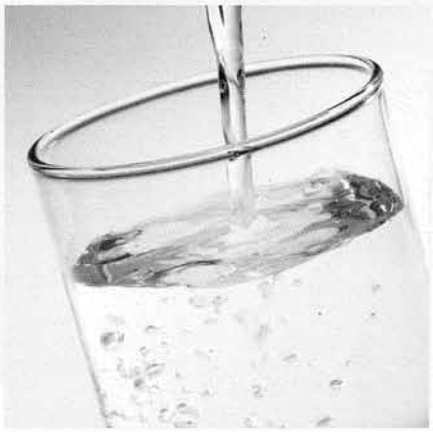

taking laxatives

With all laxatives drink at least 8-10 glasses of liquid per day which will help make the stool softer and easier to pass.

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laxatives and your bowels

If your bowel habits suddenly change for longer than two weeks, or keeps changing, check with your doctor before using a laxative.

If you have any questions about the use of laxatives, check with your practice nurse or doctor.

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the 'laxative habit'

People may overuse laxatives which may lead to a dependency on them.

Overuse of some laxatives may cause damage to the intestines and bowel function.

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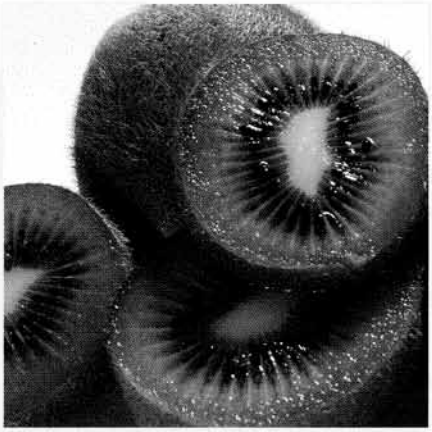
precautions when using laxatives

Don't take any type of laxative if you experience: stomach or lower abdominal pain, cramping, bloating, soreness, nausea, or vomiting.

Check with your doctor as soon as possible.

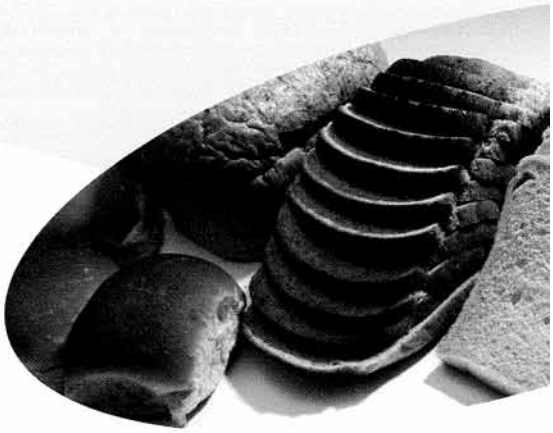


Don't take any type of laxative for more than a week unless prescribed by your doctor.

This is true even when you have had no results from the laxative.

lifelax diet and lifestyle in the management of constipation

Don't take laxatives within 2 hours of taking other medicine as the effect of the other medicine may be reduced.



Don't take laxatives if you don't need them.

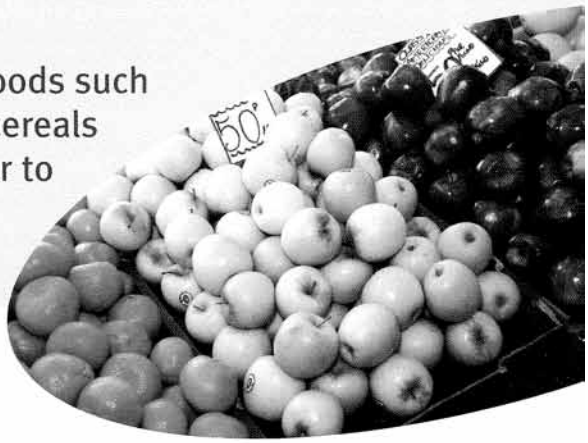
If you miss a bowel movement for a day or two – don't worry, don't take a laxative, its normal!

If you develop a skin rash while taking a laxative – check with your doctor.

diet and lifestyle in the management of constipation *lifelax*

Remember you can help your constipation by:

- Being more active: remember to drink more.
- Drinking plenty of fluid: about 8-10 cups per day – try soft drinks and not too much strong tea or coffee.
- Eating more fibre rich foods such as wholegrain breads, cereals and porridge: remember to drink plenty.



- Eating more fruit and vegetables.
- Listening to your body: go to the toilet when it tells you to and leave enough time for toileting.

You may find you have some bloating and wind at first – but as your bowel becomes used to the extra fibre this will settle down.

Follow your doctor's advice about how to take your laxatives. Laxatives are to provide short-term relief only, unless otherwise directed by a doctor.

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Appendix 4

EQ-5D self-completion questionnaire

EQ-5D – This is Euro Qual – 5D for completion by the patient.

The next few questions are how you are **at present**. *For each of the five sets of statements below please **circle the number** that **best** describes your own health state **today.***

1. **Mobility**
   - I have no problems in walking about 1
   - I have some problems in walking about 2
   - I am confined to bed.....3

2. **Self-Care**
   - I have no problems with self-care.....1
   - I have some problems washing or dressing myself.....2
   - I am unable to wash or dress myself.....3

3. **Usual Activities**
   - I have no problems with performing my usual activities (eg work, study, housework, family or leisure activities) 1
   - I have some problems with performing my usual activities.....2
   - I am unable to perform my usual activities 3

4. **Pain/Discomfort**
   - I have no pain or discomfort.....1
   - I have moderate pain or discomfort.....2
   - I have extreme pain or discomfort 3

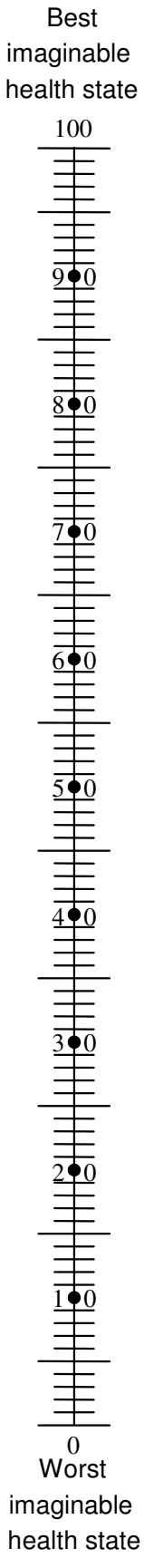
5. **Anxiety/Depression**
   - I am not anxious or depressed.....1
   - I am moderately anxious or depressed 2
   - I am extremely anxious or depressed.....3

6. Now we would like you to tell us how good or bad is your own health today, in your opinion.

   To help you say how good or bad your own health state is, we have drawn a scale (rather like a thermometer) on which the best state you can imagine is marked by 100 and the worst state you can imagine is marked by 0.

   Please draw a line from the box below to whichever point on the scale indicates how good or bad you feel your health state is **today.**

Your own health state today



Appendix 5

Adapted CONSORT e-flowchart for process evaluation

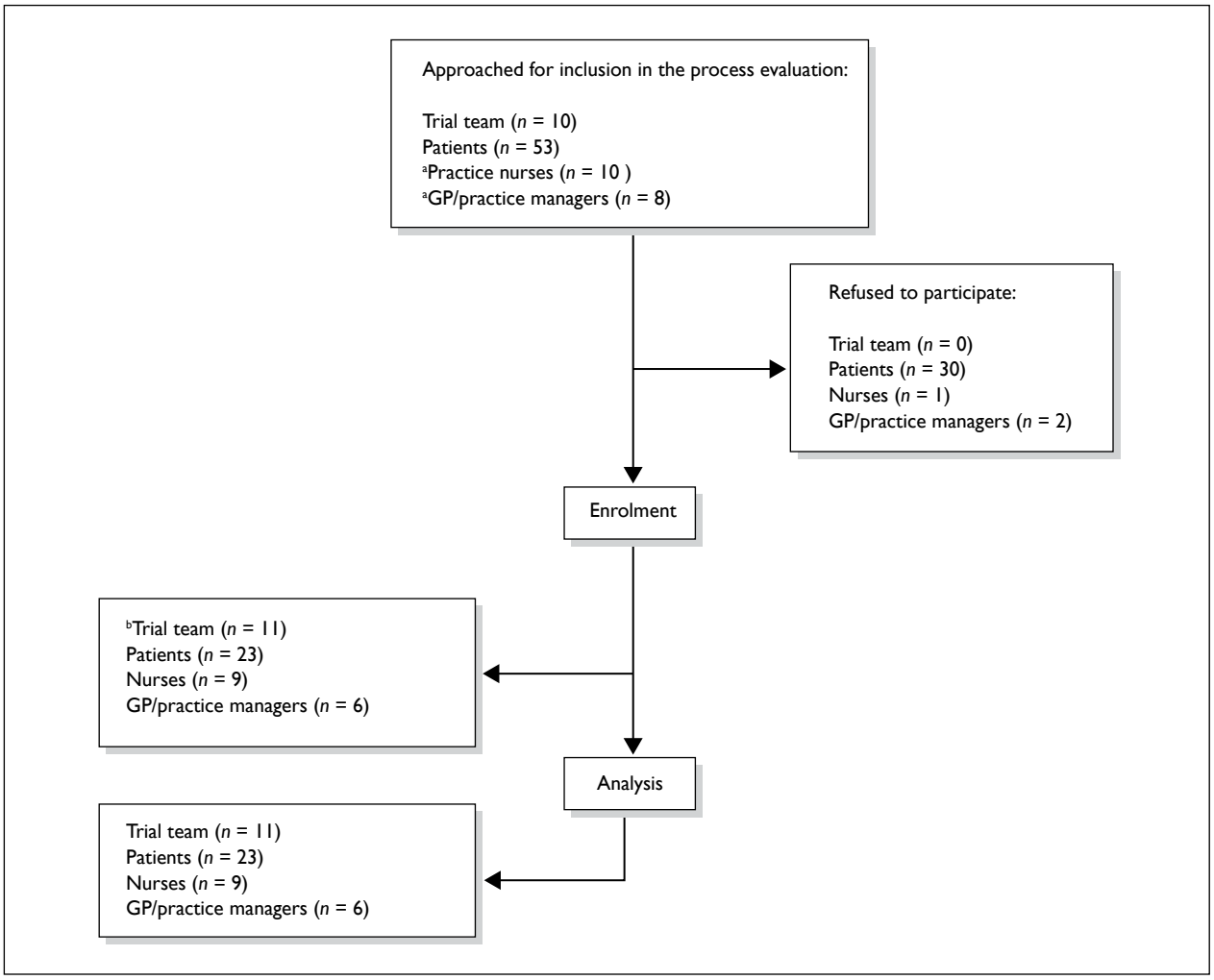


FIGURE 12 *Adapted CONSORT e-flowchart for process evaluation. a, additional practice staff were approached, but refusal was only recorded if actually given. Contact with key practice staff was sometimes never established, the researcher stopped attempts after 3–4 repeat calls. b, iterative interview with one member.*

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Feedback

The HTA programme and the authors would like to know your views about this report.

The Correspondence Page on the HTA website (www.hta.ac.uk) is a convenient way to publish your comments. If you prefer, you can send your comments to the address below, telling us whether you would like us to transfer them to the website.

We look forward to hearing from you.

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