Health Technology Assessment 2006; Vol. 10: No. 2

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M Dennis, S Lewis, G Cranswick and J Forbes, on behalf of the FOOD Trial Collaboration

January 2006

Health Technology Assessment
NHS R&D HTA Programme

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FOOD: a multicentre randomised trial evaluating feeding policies in patients admitted to hospital with a recent stroke

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Declared competing interests of authors: none

Published January 2006

This report should be referenced as follows:

Dennis M, Lewis S, Cranswick G, Forbes J. FOOD: a multicentre randomised trial evaluating feeding policies in patients admitted to hospital with a recent stroke. *Health Technol Assess* 2006;**10**(2).

Health Technology Assessment is indexed and abstracted in *Index Medicus*/MEDLINE, *Excerpta Medica*/EMBASE and *Science Citation Index Expanded (SciSearch®)* and *Current Contents®*/Clinical Medicine.

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ISSN 1366-5278

Published by Gray Publishing, Tunbridge Wells, Kent, on behalf of NCCHTA.
Printed on acid-free paper in the UK by St Edmundsbury Press Ltd, Bury St Edmunds, Suffolk.

Abstract

FOOD: a multicentre randomised trial evaluating feeding policies in patients admitted to hospital with a recent stroke

M Dennis,[1*] S Lewis,[1] G Cranswick[1] and J Forbes,[2] on behalf of the FOOD Trial Collaboration

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Objectives: To determine whether routine oral nutritional supplementation of a normal hospital diet improves outcome after stroke (Trial 1); whether early tube feeding improves the outcomes of dysphagic stroke patients (Trial 2); and if tube feeding via a percutaneous endoscopic gastrostomy (PEG) results in better outcomes than that via a nasogastric tube (NG) (Trial 3).
Design: The Feed Or Ordinary Diet (FOOD) trial was a family of three pragmatic, randomised controlled trials (RCTs). They shared facilities for randomisation, data collection, follow-up and coordination. Patients could be co-enrolled in more than one of these trials.
Setting: Patients were enrolled in 131 hospitals in 18 countries.
Participants: A total of 5033 patients who had been admitted to hospital with a recent stroke were enrolled in the trials between November 1996 and July 2003.
Interventions: In Trial 1, patients who could swallow within the first 30 days of admission were allocated to normal hospital diet versus normal hospital diet plus oral nutritional supplements (equivalent to 360 ml of 1.5 kcal/ml, 20 g of protein per day) until hospital discharge. In Trial 2, dysphagic patients enrolled within 7 days of admission were allocated to early enteral tube feeding versus avoid any enteral tube feeding for at least 1 week. In Trial 3, dysphagic patients were allocated within 30 days of admission to receive enteral tube feeding via PEG versus NG.
Main outcome measures: Survival and the modified Rankin scale (MRS), a measure of functional outcome (grade 0 indicating no symptoms and grade 5 indicating severe disability, requiring help day and night). The primary outcomes were measured 6 months after enrolment, blind to treatment allocation, by the patient or their proxy completing a postal or telephone questionnaire.
Results: In Trial 1, 4023 patients were enrolled by 125 hospitals in 15 countries. Only 314 (7.8%) patients were judged undernourished at baseline. Vital status and MRS at the end of the trial were known for 4012 (99.7%) and 4004 (99.5%), respectively. Of the 2007 allocated normal hospital diet, 253 (12.6%) died, 918 (45.7%) were alive with poor outcome (MRS 3–5) and 823 (41.1%) had a good outcome (MRS 0–2). Of the 2016 allocated oral supplements, 241 (12.0%) died, 953 (47.3%) were alive with poor outcome and 813 (40.4%) had a good outcome. The supplemented diet was associated with an absolute reduction in risk of death of 0.7% (95% CI –1.4 to 2.7; $p = 0.5$) and a 0.7% (95% CI –2.3 to 3.8, $p = 0.6$) increased risk of death or poor outcome. In Trial 2, a total of 859 patients were enrolled by 83 hospitals in 15 countries. MRS at the end of the trial was known for 858 (99.9%). At follow-up, of 429 allocated early tube feeding, 182 (42.4%) died, 157 (36.6%) were alive with poor outcome (MRS 4–5) and 90 (21.0%) had a good outcome (MRS 0–3). Of 430 allocated avoid tube feeding 207 (48.1%) died, 137 (31.9%) were alive with poor outcome and 85 (19.8%) had a good outcome. Early tube feeding was associated with an absolute reduction in risk of death of 5.8% (95% CI –0.8 to 12.5; $p = 0.09$) and a reduction in death or poor outcome of 1.2% (95% CI –4.2 to 6.6; $p = 0.7$). In Trial 3, 321 patients were enrolled by 47 hospitals in 11 countries. Of 162 allocated PEG, 79 (48.8%) died, 65 (40.1%) were alive with poor outcome and 18 (11.1%) had good outcome. Of 159 allocated NG, 76 (47.8%) died, 53 (33.3%) were alive with poor outcome and 30 (18.9%) had good outcome. PEG was associated with an increase in absolute risk of death of 1.0% (95% CI –10.0 to 11.9; $p = 0.9$) and an increased risk of death or poor outcome of 7.8% (95% CI 0.0 to 15.5; $p = 0.05$).

Conclusions: The results of Trial 1 would be compatible with oral supplementation being associated with a 1–2% absolute benefit or harm, but do not support routine supplementation of hospital diet for unselected stroke patients who are predominantly well nourished on admission. In Trial 2, the data suggest that a policy of early tube feeding may substantially reduce the risk of dying after stroke and it is very unlikely that the alternative policy of avoiding early tube feeding would significantly improve survival. Improved survival may be at the expense of increasing the proportion surviving with poor outcome. These data might usefully inform the difficult discussions about whether or not to feed a patient with a severe stroke. In Trial 3, the data suggest that in the first 2–3 weeks after acute stroke, better functional outcomes result from feeding via NG tube than PEG tube, although there was no major difference in survival. These data do not support a policy of early initiation of PEG feeding in dysphagic stroke patients. Future research might be focused on making NG tube feeding safer and more effective, also studies need to confirm the increased risk of gastrointestinal haemorrhage associated with tube feeding and, if confirmed, establish whether any interventions might reduce this risk. Future work might also aim to establish why worse functional outcomes occurred in PEG-fed patients because patients with prolonged dysphagia or intolerance of an NG tube are inevitably fed via a PEG tube.

Contents

List of abbreviations

BMI	body mass index
CI	confidence intervals
DMC	Data Monitoring Committee
FOOD	Feed Or Ordinary Diet
GI	gastrointestinal
HRG	Healthcare Resource Grouping
HRQoL	health-related quality of life
IQR	interquartile range
ITT	intention-to-treat
LOS	length of stay
MRS	modified Rankin scale
NG	nasogastric tube
NHD	normal hospital diet
NHD+S	normal hospital diet plus oral supplements
OHS	Oxford Handicap Scale
OR	odds ratio
PEG	percutaneous endoscopic gastrostomy
QALY	quality-adjusted life-year
QoL	quality of life
QTE	quartile treatment effect
RCT	randomised controlled trial
SD	standard deviation
SE	standard error
TIA	transient ischaemic attack
TPN	total parenteral nutrition

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 at the end of the table.

Executive summary

Objectives

Undernutrition is common among patients admitted to hospital with acute stroke. It may develop, or worsen, during hospitalisation, and is independently associated with poor outcomes. We aimed to answer three questions about feeding stroke patients in hospital:

1. Does routine oral nutritional supplementation of a normal hospital diet improve outcome after stroke?
2. Does early tube feeding improve the outcomes of dysphagic stroke patients?
3. Does tube feeding via a percutaneous endoscopic gastrostomy (PEG) result in better outcomes than that via a nasogastric tube (NG).

Design

The Feed Or Ordinary Diet (FOOD) trial was a family of three pragmatic, randomised controlled trials (RCTs). They shared facilities for randomisation, data collection, follow-up and coordination. Patients could be co-enrolled in more than one of these trials.

Setting

Patients were enrolled in 131 hospitals in 18 countries.

Participants

A total of 5033 patients who had been admitted to hospital with a recent stroke were enrolled in the trials between November 1996 and July 2003.

Interventions

In Trial 1, patients who could swallow within the first 30 days of admission were allocated to normal hospital diet versus normal hospital diet plus oral nutritional supplements (equivalent to 360 ml of 1.5 kcal/ml, 20 g of protein per day) until hospital discharge. In Trial 2, dysphagic patients enrolled within 7 days of admission were allocated to early enteral tube feeding versus avoid any enteral tube feeding for at least 1 week. In Trial 3, dysphagic patients were allocated within 30 days of admission to receive enteral tube feeding via PEG versus NG.

Main outcome measures

The primary outcome was based on survival and the modified Rankin scale (MRS), a measure of functional outcome (grade 0 indicating no symptoms and grade 5 indicating severe disability, requiring help day and night). The primary outcomes were measured 6 months after enrolment, blind to treatment allocation, by the patient or their proxy completing a postal or telephone questionnaire.

Results

Trial 1: normal hospital diet versus normal hospital diet plus oral supplements

In all, 4023 patients were enrolled by 125 hospitals in 15 countries. This represents 67% of our original target of 6000 patients. Only 314 (7.8%) of patients were judged undernourished at baseline. Vital status and MRS at the end of the trial were known for 4012 (99.7%) and 4004 (99.5%), respectively. Of the 2007 allocated normal hospital diet, 253 (12.6%) died, 918 (45.7%) were alive with poor outcome (MRS 3–5) and 823 (41.1%) had a good outcome (MRS 0–2). Of the 2016 allocated oral supplements, 241 (12.0%) died, 953 (47.3%) were alive with poor outcome and 813 (40.4%) had a good outcome. The supplemented diet was associated with an absolute reduction in risk of death of 0.7% (95% CI –1.4 to 2.7; $p = 0.5$) and a 0.7% (95% CI –2.3 to 3.8, $p = 0.6$) increased risk of death or poor outcome.

Trial 2: early enteral tube feeding versus avoid enteral tube feeding

A total of 859 patients were enrolled by 83 hospitals in 15 countries, 43% of our original target of 2000. MRS at the end of the trial was known for 858 (99.9%). At follow-up, of 429 allocated early tube feeding, 182 (42.4%) died,

157 (36.6%) were alive with poor outcome (MRS 4–5) and 90 (21.0%) had a good outcome (MRS 0–3). Of 430 allocated avoid tube feeding 207 (48.1%) died, 137 (31.9%) were alive with poor outcome and 85 (19.8%) had a good outcome. Early tube feeding was associated with an absolute reduction in risk of death of 5.8% (95% CI –0.8 to 12.5; $p = 0.09$) and a reduction in death or poor outcome of 1.2% (95% CI –4.2 to 6.6; $p = 0.7$).

Trial 3: NG tube feeding versus PEG tube feeding

In this trial, 321 patients were enrolled by 47 hospitals in 11 countries, 32% of our original target of 1000 patients. Of 162 allocated PEG, 79 (48.8%) died, 65 (40.1%) were alive with poor outcome and 18 (11.1%) had good outcome. Of 159 allocated NG, 76 (47.8%) died, 53 (33.3%) were alive with poor outcome and 30 (18.9%) had good outcome. PEG was associated with an increase in absolute risk of death of 1.0% (95% CI –10.0 to 11.9; $p = 0.9$) and an increased risk of death or poor outcome of 7.8% (95% CI 0.0 to 15.5; $p = 0.05$).

Conclusions

Implications for healthcare

In Trial 1, we were unable to confirm the expected 4% absolute benefit for death or poor outcome from routine oral nutritional supplements. Our results would be compatible with oral supplementation being associated with a 1–2% absolute benefit or harm, but do not support routine supplementation of hospital diet for unselected stroke patients who are predominantly well nourished on admission.

In Trial 2, our data suggest that a policy of early tube feeding may substantially reduce the risk of dying after stroke and it is very unlikely that the alternative policy of avoiding early tube feeding would significantly improve survival. Improved survival may be at the expense of increasing the proportion surviving with poor outcome. These data might usefully inform the difficult discussions about whether or not to feed a patient with a severe stroke.

In Trial 3, our data suggest that in the first 2–3 weeks after acute stroke, better functional outcomes result from feeding via NG tube than PEG tube, although we found no major difference in survival. These data do not support a policy of early initiation of PEG feeding in dysphagic stroke patients.

Recommendations for research

We think it is unlikely that the stroke community will have the 'appetite' for further and much larger RCTs assessing these interventions. This view is based on our surveys of clinicians' views and the fact that avoiding tube feeding (Trial 2) and early PEG (Trial 3) are so unlikely to have a clinically significant benefit for patients.

Future research might be focused on making NG tube feeding safer and more effective by optimising methods of: insertion, confirmation of correct placement and retention of tubes. Also, studies need to confirm the increased risk of gastrointestinal haemorrhage associated with tube feeding and, if confirmed, establish whether any interventions might reduce this risk. Our finding that PEG tube feeding was associated with worse functional outcomes was unexpected and not easily explained. Future work might also aim to establish why these worse outcomes occurred in PEG-fed patients because patients with prolonged dysphagia or intolerance of an NG tube are inevitably fed via a PEG tube.

Chapter 1
Introduction

Background

In the UK, approximately 130,000 people suffer a stroke each year, which commonly leads to death or serious disability. Poor nutrition is a common and under-recognised problem in patients admitted to hospital and also in those who remain in hospital for prolonged periods.[1–4] It is particularly frequent among elderly patients and has been associated with reduced muscle strength, reduced resistance to infection and impaired wound healing. Among patients with stroke, most of whom are elderly, muscle weakness, infections and pressure sores are common and account for significant mortality and morbidity.[5] The reported frequency of malnutrition amongst hospital-admitted stroke patients varies between 8 and 40%, although much of this variation may be due to differences in case mix, the definitions of malnutrition and the methods of assessment.[6–12]

Undernutrition on admission may be compounded by the problems that stroke patients have with feeding. Dysphagia occurs in up to 50% of hospital-admitted stroke patients.[13–17] Patients may not be able to protect their airway or cough effectively. This can lead to aspiration of any fluid or food given orally, or even aspiration of their own saliva. Pneumonia, lung abscess or death may result. Also, unless alternative methods of hydrating and feeding patients are employed, dysphagia will result in dehydration and worsening nutrition. Fortunately, dysphagia usually improves over the first few days or weeks so that only a very small minority of patients will survive with persistent dysphagia.

Even those patients who do not have dysphagia may have other problems which may impair their ability to take in adequate nutrition. Poor arm function and sitting balance will make feeding slow or difficult. Facial weakness may make chewing difficult and dentures may not fit. Unfortunately, dentures often go missing whilst patients are in hospital. Many patients suffer poor appetite associated with intercurrent illness or drugs. Poor quality hospital food which is not very palatable may compound these problems.

Several studies have shown that nutritional status may deteriorate during hospital admission in a significant minority of patients.[8,11,15,18] This is of concern because undernutrition has been shown to be associated with poorer outcomes after stroke – longer lengths of stay, worse survival and less good functional recovery.[11,12,19]

A range of interventions may help to identify and alleviate feeding problems and help to prevent or treat undernutrition. Some of these are simple, make sense and are unlikely to be associated with adverse effects. Thus the introduction of routine swallow screens and nutritional assessment has been advocated,[20–22] although most hospitals struggle to perform these assessments in all patients. It seems sensible to ensure that the hospital food is nutritionally adequate, palatable and can be provided in suitable forms to suit patients with mild to moderate dysphagia. Stroke patients often benefit from thickened fluids to reduce the risk of aspiration and food of modified consistency (e.g. minced or mashed). Nurses, dieticians and speech and language therapists are all involved in trying to optimise patients' intake. Beyond these simple and common-sense interventions, there are others which may seem sensible but have significant costs or the likelihood of adverse effects. For example, theoretically, feeding patients in the acute stage of stroke might be associated with metabolic changes (e.g. hyperglycaemia), which could be detrimental to the ischaemic penumbra.[23] There is evidence in animal models that increased blood sugar in the acute phase of stroke may increase cerebral damage and in humans hyperglycaemia is associated with worse survival and functional outcomes. Widely used interventions to improve nutritional intake are outlined below.

Oral nutritional supplements for those without significant dysphagia

There is a wide range of supplements, of varying consistency (liquid, puddings) and formulae (milk

FIGURE 1 *Photograph of commercially available pack of oral sip feed*

protein based, fruit juice based). Not all are nutritionally complete but most provide additional calories and protein. Typically these are presented to patients in Tetrabricks™ (*Figure 1*). Several studies have reported that even when given, supplements are often not consumed (e.g. being out of reach of the patient or placed at the bedside on the affected side) or, if they are consumed, reduce the quantity of meals taken. One study recommended that supplements should be prescribed on the drug chart and decanted from the carton. In addition, the dosage should be split into three small doses throughout the day in order to maximise the quantity of meals taken.[24]

A systematic review of randomised controlled trials (RCTs) of so-called 'oral sip feeds' given to elderly patients has indicated that their use improves nutritional status and may also reduce case fatality.[25,26] However, all these trials were small, single-centre studies, which are more prone to various biases.

Only one small randomised trial ($n = 40$) has suggested that oral supplementation after stroke improves nutritional parameters.[27] This trial was too small to indicate whether nutritional supplements improved survival or functional outcomes.

Enteral tube feeding for those with dysphagia

The most established method of enteral tube feeding is nasogastric (NG); however, more recently, percutaneous endoscopic gastrostomy (PEG) feeding has been introduced as an alternative method.

NG feeding involves the insertion of a fine-bore feeding tube via the nasal passage to the stomach through which artificial feeds are typically pumped using a specialised pump (*Figure 2*). In patients who are unable to swallow, NG tubes are not always easy to insert and, perhaps because they are uncomfortable, they are often pulled out and have to be replaced. Prior to feeding, the placement of the tube needs to be confirmed via a chest X-ray or aspiration of gastric fluids. Misplaced tubes may lead to feed going into the lung to cause pneumonia or even death (*Figure 3*, showing a tube in the right lower lobe). There has even been one case described of a tube being inserted through the cribriform plate into the ventricles of the brain. Patients typically find the insertion uncomfortable and they frequently pull out the tubes, which leads to interruption of feeding, fluids and medication. Some hospitals use restraints, including mittens, stitches through the nose or tying hands to cotsides to reduce the risk of tube displacement (*Figure 4*). If left *in situ* for prolonged periods, ulceration of the nostril, oesophageal strictures and oesophagotracheal fistulae have been described.

In recent years, a number of alternative methods of enteral tube feeding have been developed. Nasojejunal tubes have been advocated as less likely to be associated with gastro-oesophageal reflux and thus aspiration. Insertion of a tube through the

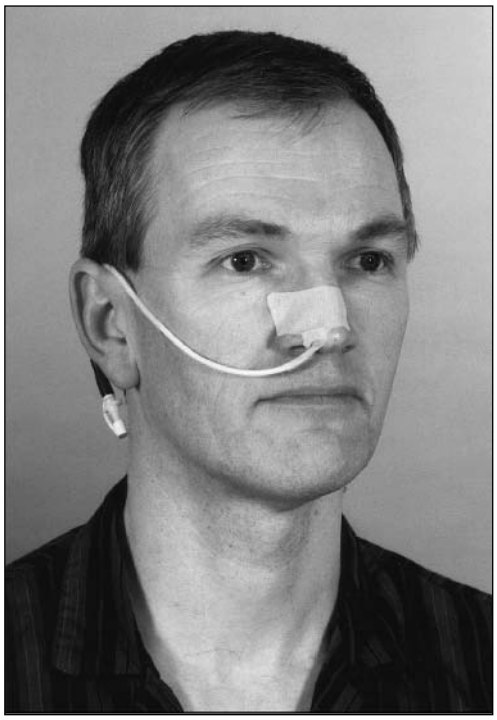

FIGURE 2 *Photograph of an NG tube in place*

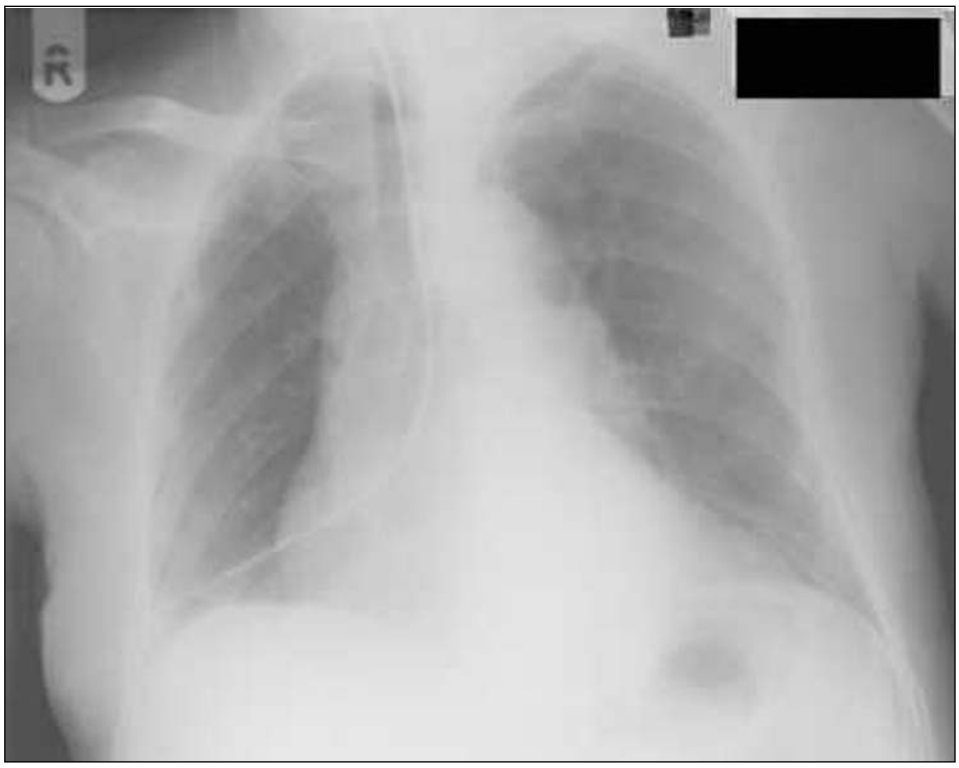

FIGURE 3 *Chest radiograph showing an NG tube mispositioned in right lower lobe of lungs*

abdominal wall into the stomach (percutaneous gastrostomy) (*Figure 5*) or jejunum (jejunostomy) avoids the need for the tube to pass through the nose. Tubes are inserted endoscopically (i.e. PEG) or radiologically to increase the likelihood of correct placement. Once in place, PEGs appear to be more acceptable to patients than NG tubes. They are rarely pulled out and can be left in place for months or even years. However, their insertion usually requires the patient to be sedated and this is associated with a risk of aspiration. Also, as with most surgical procedures, infection, bleeding and perforation are important and potentially fatal complications. *Table 1* provides estimates from the literature of the frequency of these complications in stroke patients and other elderly patients fed via

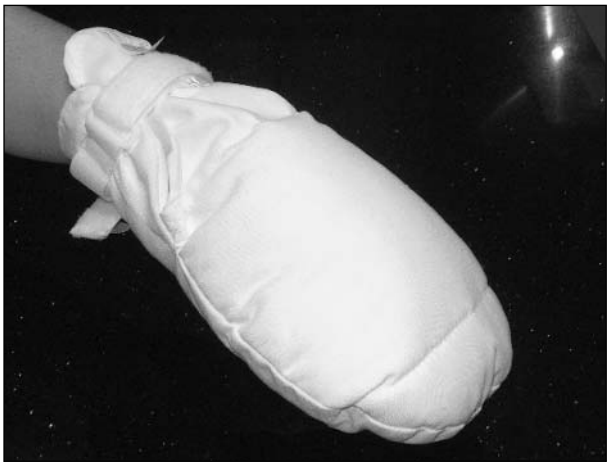

FIGURE 4 *Mittens sometimes used to help retain NG tubes in confused and agitated patients*

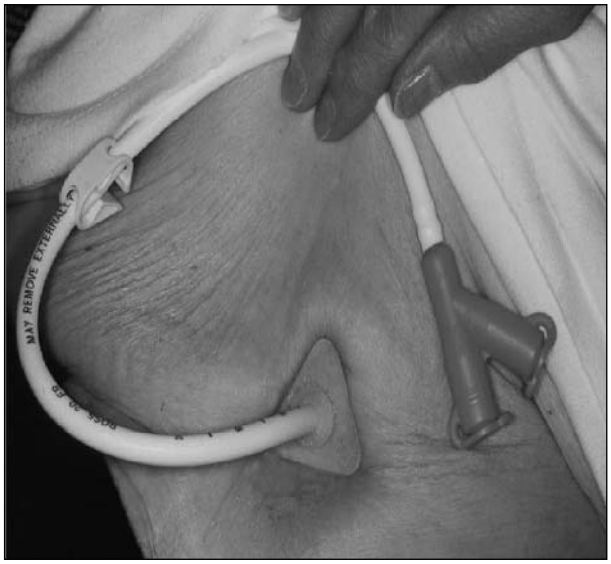

FIGURE 5 *A PEG tube in place*

TABLE 1 *Complication rates with PEG taken from a systematic review of published studies (Wiggam and colleagues, 2001[28])*

Complication	Stroke only:[31,33,34,35,36] *N* = 310 (%)	All patients[28] (personal communication[b]): *N* = 11,370 (%)
Pneumonia	19	11[a]
Tube blockage/breakage or removal	11	5.2
Wound infection	8	2.8
Gastrointestinal haemorrhage	0.6	0.4
Gut perforation/peritonitis	0.3	0.5

[a] *n* = 2843.
[b] Personal communication, Wiggam I.

PEG tube.[28] The systematic review suggested that there was a 0.3% risk of death related to the procedure itself and a 10% risk of major complications [which may well be underestimated given that (1) specialist centres which achieve better results are more likely to publish than those with less interest or higher complication rates, (2) many studies are retrospective and rely on routine recording of complications and (3) stroke patients who tend to be elderly and frail may have higher complication rates].

Hence although insertion of a feeding tube may allow patients' nutritional needs to be met, any benefit from this may be offset by the complications of the tube feeding. To date, there have been no RCTs to determine the balance of risk and benefit of NG tube feeding in stroke patients. By 1996 there had been just three small randomised trials that compared NG and PEG tube feeding and only one of these was specifically in stroke patients. These suggested that PEG provided more effective nutritional support with less interruption of feeding.[29–31] The trial in stroke patients showed that those fed by PEG had an implausibly large (70% relative) reduction in case fatality compared with those fed via NG tube.[31] However, this trial only included 30 patients and few data were provided to allow an assessment of the effectiveness of randomisation in achieving balanced groups. It seems most likely that some imbalance in baseline factors accounted for much of the observed difference in outcome. There is little doubt that a PEG tube is a better option if feeding is to be prolonged. Also, in practice, there may be no alternative to a PEG tube if artificial feeding is required and NG feeding has been unsuccessful.

Variation in practice

A survey of almost 3000 physicians who manage stroke in the UK demonstrated wide variations in the use of oral supplements and in the timing and method of feeding in patients with dysphagia following a stroke.[32] In this survey, about 45% of clinicians reported using oral nutritional supplements whereas the majority of the remainder were uncertain of their benefits. About 60% of clinicians reported starting tube feeding within the first week after stroke whereas the remainder delayed longer. About 90% preferred an NG tube initially, although after the first week 75% preferred feeding via a PEG tube. Such variations reflected the lack of clear evidence to guide practice.

In order to provide evidence, the Feed Or Ordinary Diet (FOOD) Trial aimed to answer the following three questions:

1. In patients who can take adequate oral fluids, does routine oral nutritional supplementation increase the proportion of patients with stroke surviving without disability?
2. In patients who are unable to take an adequate diet orally, does early initiation of tube feeding (NG or PEG) increase the proportion of patients with stroke surviving without severe disability? Delay of tube feeding would inevitably lead to poorer nutritional intake but also would avoid the risks of tube feeding in a significant number of patients in whom dysphagia rapidly improves.
3. In patients who need tube feeding, is a PEG tube, instead of the traditional NG tube, associated with improved outcomes after stroke?

Chapter 2
Methods

Overview

The FOOD Trial was a family of three pragmatic multicentre, international RCTs evaluating different feeding policies in patients with a recent stroke. These trials shared similar randomisation, follow-up and data collections systems.

Trial 1 included patients who were able to swallow within the first 30 days of admission and compared the outcomes of those given a normal hospital diet with those given oral supplements in addition to the normal hospital diet.

Trial 2 included patients who were unable to swallow within the first 7 days of hospital admission and compared the outcomes of those given enteral tube feeding early after admission with those in whom enteral tube feeding was avoided for at least 1 week.

Trial 3 included patients who were unable to swallow and compared the outcomes of those given enteral tube feeding via a PEG with those fed via an NG.

Objectives

The three primary research questions were as follows:

1. In patients who can take adequate oral fluids, does routine oral nutritional supplementation increase the proportion of patients with stroke surviving without disability? (Trial 1).
2. In patients who are unable to take an adequate diet orally, does early initiation of tube feeding (NG or PEG) increase the proportion of patients with stroke surviving without severe disability? (Trial 2).
3. In patients who need tube feeding, is a PEG tube, instead of the traditional NG tube, associated with improved outcomes after stroke? (Trial 3).

In addition, secondary questions were as follows:

- Whether any feeding policy might reduce the case fatality rate but only at the expense of increasing the proportion of patients surviving with severe disability?
- Whether the feeding policy has any major effects on the utilisation of hospital facilities and the final placement of patients?
- Whether any advantage from nutritional supplementation applies to all patients with stroke or only to certain subgroups such as the elderly or previously malnourished?

Participating centres

Any hospital that admitted patients with a recent stroke could participate in the FOOD Trial if the team responsible for patient care was uncertain as to the use of oral supplements in those patients who were able to swallow and/or the timing or type of tube feeding to use in patients with dysphagia.

The FOOD Trial was coordinated from the Neurosciences Trials Unit at the Western General Hospital in Edinburgh, where all completed data collection forms were sent for data entry and storage.

Eligibility criteria

Inclusion criteria

1. admission to hospital with a stroke (first or recurrent stroke) within 7 days of onset

OR

2. suffering a stroke whilst already in hospital

AND

3. randomising clinician substantially uncertain about the best feeding policy

AND

4. consent or assent from close relatives obtained.

Eligible patients could be randomised into Trials 1 and/or 3 within the first 30 days of hospital admission (or stroke onset if it occurred as an inpatient). Trial 2 patients could be randomised within the first 7 days of hospital admission (or stroke onset if it occurred as an inpatient).

Exclusion criteria

1. patients with subarachnoid haemorrhage

OR

2. Patients who, in the opinion of the responsible clinician, were unlikely to benefit from one of the trial interventions, such as
   (a) patients who experienced a transient ischaemic attack (TIA) or trivial stroke and were likely to remain in hospital for only a few days
   (b) patients who could swallow but in whom nutritional supplementation was contraindicated (e.g. morbidly obese patients)
   (c) those in coma (i.e. unresponsive to pain) or who were very unlikely to survive more than a few days because of some severe non-stroke illness.

OR

   (d) patients who have already been entered into the same FOOD Trial.

Consent

In the UK, Multicentre Research Ethical Committee (MREC) Approval was granted and each individual centre obtained Local Research Ethical Committee (LREC) Approval. Outwith the UK, appropriate ethical approval was sought and granted.

Where possible, informed consent was obtained when the patient was able to understand and communicate effectively. Alternatively, a close relative was able to give approval/agreement to participate in the trial. If the patient was unable to express his/her wishes and there were no close relatives, an independent clinician was sought to provide approval/agreement.

A patient information booklet (Appendix 7) was provided to patients (or their carers) which described the aims of the trial and the potential risks and benefits of the feeding policies. In many cases the booklet was supplemented with photographs illustrating the alternative feeding regimes. The patients (or their carers) were given time to consider the trial fully and ask any questions they had about the implications of the trial.

Interventions

Trial 1: normal hospital diet versus normal hospital diet plus oral supplements

Patients who passed a swallow screen could be randomised within the first 30 days of admission to receive either the normal hospital diet (NHD) or a nutritional supplement in addition to the NHD. NHD was that which was normally provided to patients in that hospital and could be of altered consistency (e.g. for those with some swallowing difficulties) or composition (e.g. for patients with special needs, such as diabetics). For patients randomised to NHD, nutritional supplements were not to be prescribed on their drug chart, although, if supplementation was the norm in a hospital, this might be continued as long as patients allocated normal hospital diet plus oral supplements (NHD+S) received the prescribed supplement in addition to those routinely given. The oral supplement was that which was usually given at the institution, which contained 1.5 kcal/ml. Three doses of 120 ml were to be given daily and prescribed on the drug chart. This involved decanting the supplement into a cup, which had the advantage over sucking the supplement from the 200-ml carton through a straw that one could see that the liquid was taken. This amount of supplement had previously been shown to increase the net calorie intake of elderly patients in hospital without substantially reducing their intake of hospital diet.[24] During the trial, a greater range of supplements with this nutritional density but different consistencies (puddings, yoghurts) became available, which allowed patients with some swallowing problems to be enrolled.

Trial 2: Early enteral tube feeding versus avoid enteral tube feeding

Eligible patients could be randomised within the first 7 days of their admission (or in-hospital stroke) between early tube feeding (NG or PEG) versus avoid tube feeding for at least 1 week. If allocated early tube feeding, this was to be initiated as soon as possible after randomisation and preferably within 3 days of the randomisation telephone call. NG tubes could be of either wide or small bore (although the latter were more commonly used) and inserted following local guidelines. Percutaneous tubes were inserted endoscopically or radiologically into the stomach or jejunum according to local practice. The liquid feed was that normally used at that institution and we recommended that it should be given in consultation with a dietitian.

Patients randomised to avoid tube feeding were to avoid tube feeding for at least 1 week from the time of randomisation but hydrated using parenteral fluids (intravenous or subcutaneous fluids) given in accordance with local protocols. Total parenteral nutrition (TPN) was not to be given. At the end of this week, the randomising clinician could then decide if and when tube feeding should start.

In all cases, it was acceptable for patients to take food or fluid orally if their swallowing improved to allow this. If adequate to meet the needs of the patients, any tube feeding could be stopped.

Trial 3: NG tube feeding versus PEG tube feeding

Patients could be randomised between NG feeding and PEG feeding within the first 30 days of the hospital admission or within 30 days of a stroke occurring in hospital. Tube feeding was to be initiated as soon as possible after randomisation and preferably within 3 days of the randomisation telephone call. NG tubes were of either wide or small bore and inserted following local guidelines. Percutaneous tubes were inserted endoscopically or radiologically, into the stomach or jejunum according to local practice. The liquid feed which would normally be used at that institution was given, in consultation with a dietitian.

Co-enrolment

Collaborating centres were encouraged to co-enrol their patients into more than one of the three trials if the clinicians were substantially uncertain about more than one of the feeding policies being tested. Patients could be co-enrolled:

- At the same time in Trial 2 (early tube versus avoid) and Trial 3 (NG versus PEG) if the randomising clinician was unsure about both the timing and type of tube feeding.
- Sequentially in Trial 2 (early tube versus avoid) then Trial 3 (NG versus PEG) if the patient's swallowing did not recover.
- Sequentially in Trial 2 (early tube versus avoid) then Trial 1 (NHD versus NHD+S) if the patient's swallowing improved.
- Sequentially in Trial 3 (NG versus PEG) then Trial 1 (NHD versus NHD+S) if the patient's swallowing improved.
- Into all three trials, i.e. Trial 2 (early tube versus avoid) in the first week, Trial 3 (NG versus PEG) if dysphagia persisted and then Trial 1 (NHD versus NHD+S) if swallowing improved within the first 30 days.

Patients could not be randomised into the same trial twice.

Duration of feeding regimens

If allocated, oral supplements were to be prescribed until hospital discharge. However, the responsible clinician could stop supplements earlier if this was clinically necessary (e.g. excessive weight gain) and record the reason on the discharge form (Appendix 4).

If a patient was allocated to avoid tube feeding, intravenous or subcutaneous fluids were to continue for 7 days unless they could take adequate fluids orally. Thereafter, the responsible clinician could re-randomise the patient or decide how best to feed them. If allocated early tube feeding (NG or PEG), this was to continue until death or until the responsible clinician did one of the following:

- Decided that the patient was taking an adequate oral diet (i.e. the dysphagia had resolved).
- Established that further tube feeding was futile.
- Was required to use the alternative tube (e.g. in cases where a patient repeatedly pulled out an NG tube, it was acceptable to insert a PEG).

Patients could be discharged home with a feeding tube in place when necessary.

Baseline data

The baseline data were collected by the randomising clinician on to a form (Appendix 2). This included patient identifiers, factors included in our minimisation algorithm, patients' ability to swallow and their nutritional status. All data were captured by our randomisation system before treatment allocation.

A simple 'end of the bed' assessment of nutritional status was developed and tested prior to the start of recruitment into FOOD to establish its validity and reliability.[19,37] This simple assessment could be used in any hospital setting since no equipment or specific training was necessary. Use of this measure ensured that nutritional assessment was not a barrier to participation. Centres could, if they wished, perform additional tests to assess patients' status further if required, but these data were not recorded in detail.

Randomisation

A central 24-hour telephone randomisation service was provided for this trial. For the pilot phase, the Clinical Trials Services Unit in Oxford provided this service, and thereafter a suite of in-house systems was developed to provide a 24-hour service:

- A 'manual desktop service', which operated during office hours. Callers were put through to

a member of the trial coordinating team, who entered the baseline data into a dedicated computer system.
- An automated service primarily for use outwith office hours. This sophisticated system captured data via sound and keypad strokes.
- An Italian language version of the automated service
- A 'palmtop'-based version (FLIP) for use as an emergency back-up [this was carried by the Principal Investigator along with the 24-hour helpline in order that patients could be randomised outwith office hours if the automated randomisation service was not available (e.g. in the event of a computer failure or power cut)]. An in-house computer programmer developed this system, which used simple randomisation rather than minimisation to allocate treatments. The patient baseline details and treatment allocation were then entered into the trial database on the next working day so that the minimisation system could take account of it.

Sequence generation

The system employed a computer-generated minimisation algorithm which balanced treatments within each country and used age (greater than or less than 75 years), sex and predicted probability of poor outcome (<80%, >80% probabilities) as stratification variables. The predicted probability was based on a well-validated and reliable outcome prediction model consisting of six variables (age, pre-stroke independence, pre-stroke living alone, able to lift both arms off the bed, able to walk independently and able to talk without being confused).[38–41]

On entering these data into the computer system, a treatment would be automatically assigned which would ensure balance of these variables between the treatment groups.

Allocation concealment

For all methods of randomisation, data had to be entered and verified before the computer program could automatically generate a treatment allocation. It was impossible to guess the allocation given the use of minimisation to balance treatments between groups.

The randomisation systems were housed on a secure server with access permitted, via a password, only to those members of the coordinating team who had been fully trained how to use the systems. Participating centres were issued with codes in order for them to access the randomisation services (three separate numerical codes).

Follow-up

A simple four-page discharge form (Appendix 4) was completed by the local coordinator on discharge from hospital, transfer out of the randomising centre or death, whichever occurred first. Data collected included the feeding start and finish dates, the route of enteral feeding (NG or PEG) and the numbers of tubes inserted, the reasons for stopping and any complications of feeding or of stroke. Only complications that occurred after randomisation and prior to discharge or in-hospital death were collected. These forms were not completed explicitly blind to baseline nutritional status or treatment allocation. Forms were sent to the coordinating centre for input into the computer system.

Adverse events in hospital

Major complications of the feeding regimens were reported at once on a report card (Appendix 3) to the coordinating centre and were reviewed by the Principal Investigator.

Final follow-up

Final follow-up was performed to establish the patients' vital status, functional ability, place of residence, current method of feeding and quality of life (QoL). It was performed about 6 months after randomisation, blinded to treatment allocation and after confirmation had been sought from the patient's GP that follow-up was appropriate (i.e. the patient was still alive). If patients were unable to complete it, then the information was collected from a carer or proxy.

Each national coordinating centre collected follow-up information, usually by means of a postal questionnaire (Appendix 5) or structured telephone interview. In some countries, patients were followed up in an outpatient clinic (e.g. Singapore) or at home by a blinded assessor (e.g. India). In general, however, personalised follow-up questionnaires (with accompanying letters and written in the appropriate language) were sent out

2 weeks in advance of the follow-up date. If completed questionnaires were not returned within 3 weeks, another copy was sent. If this was not returned, further attempts were made to contact the patient by telephone in order to complete the follow-up form [e.g. in the UK the Principal Investigator attempted to contact them (or a member of their family or support network)]. If the patient was still in hospital or had been admitted to hospital at the time of follow-up, an 'in-hospital' follow-up form was sent for completion in the UK only. In other countries, the national coordinator arranged for the 6-month follow-up form to be completed. If a follow-up was late then the patient's status at that time was recorded unless the patient had died before, in which case the date of death was recorded. If follow-up was greatly delayed and the patient had died after 6 months, available information regarding the patient's functional status at 6 months was collected if possible.

Outcomes

The primary outcome of all trials was based on the Oxford Handicap Scale (OHS), or Modified Rankin Scale (MRS).[42] We refer to the MRS as the more widely used term in the remainder of this report.

Primary outcomes

Sample-size calculations were based on a dichotomous outcome – death or poor outcome at follow-up. The cut-off value for poor outcome was MRS 3–5 in Trial 1 and MRS 4–5 in Trials 2 and 3, where an MRS of 3 in a dysphagic patient would be regarded as a good outcome given the associated stroke severity. The two primary analyses are based on 'death or poor outcome' and overall survival, subdivided by allocated treatment, irrespective of compliance. We use the terms 'good outcome' and 'poor outcome' throughout this report as a convenient shorthand, but acknowledge that patients will apply their own judgement so that for some survival in any state might be 'good' whereas for others any degree of disability may be 'poor'.

Secondary outcomes

Outcomes collected blind to treatment allocation included place of residence and the EUROQoL measure of health-related quality of life (HRQoL), from which a utility score was derived.[43,44] Other secondary outcomes were collected but not blinded to treatment allocation. These included compliance with treatment, length of hospital stay, discharge destination, specified in-hospital complications and cause of death.

Additional secondary outcomes

These were:

- proportion of patients who were dead at 6 months
- HRQoL among survivors
- time to hospital discharge
- length of stay (LOS) in hospital (which will provide a surrogate outcome for analysis of cost)
- number of days of tube feeding
- adverse effects of feeding regimes
- premature cessation of feeding regimes and reasons.

Blinding

FOOD was an open trial, with both the randomising person and the patient being aware of the treatment allocation. The only blinded assessment was the 6-month follow up.

Calculation of sample size

The sample size calculations were based on data from the Lothian Stroke Register, a hospital-based stroke register which suggested that the ability to swallow was a powerful prognostic factor (*Table 2*). Indeed, of the 171 patients who were unable to swallow on or soon after admission, >40% had died within the 6-month period following the stroke compared with <9% in those patients who could swallow.

The effect sizes chosen for the calculations of sample size represented a judgement about what was plausible, based on other treatments in stroke. We did not base them on previous trials or systematic reviews[25,31] since we judged these to have produced overly optimistic estimates of effect size.

Trial 1: normal hospital diet versus normal hospital diet plus oral supplements

To detect an increase in the proportion of patients surviving free of dependency (MRS <3) from 52 to 56%, we planned to enrol at least 6000 patients to provide 80% power, when the null hypothesis is rejected at p-values of ≤0.05 (i.e. $\alpha = 0.05$, $\beta = 0.2$). Patients were divided equally between the two groups.

TABLE 2 *Data from the Lothian Stroke Register showing the number and proportion of patients with different 6-month outcomes on the MRS according to whether they were able to swallow shortly after hospital admission*

	Non-swallowers			Swallowers		
MRS	***n***	**%**	**Cumulative %**	***n***	**%**	**Cumulative %**
1 or 2	28	16.4	16.4	247	51.7	51.7
3	24	14.0	30.4	109	22.8	74.5
4	32	18.7	49.1	45	9.4	83.9
5	18	10.5	59.6	35	7.3	91.2
6 (dead)	69	40.4	100	42	8.8	100

Trial 2: Early enteral tube feeding versus avoid enteral tube feeding

In order to detect an increase in the proportion of patients surviving free of severe disability (MRS <4) from 30 to 36%, we aimed to enrol at least 2000 patients to provide 80% power, when the null hypothesis is rejected at p-values of ≤ 0.05 (i.e. $\alpha = 0.05$, $\beta = 0.2$). Patients were split evenly between the two treatment arms.

Trial 3: NG tube feeding versus PEG tube feeding

In order to detect an increase in the proportion of patients surviving free of severe disability (MRS <4) from 30 to 39%, we planned to randomise at least 1000 patients divided equally between the two groups to provide 80% power, when the null hypothesis is rejected at p-values of ≤ 0.05 (i.e. $\alpha = 0.05$, $\beta = 0.2$).

In the event that the sample size was reached in one arm of the trial, recruitment was to continue until the sample size was reached in the other arms of the trial unless the independent Data Monitoring Committee (DMC) advised otherwise.

Data checking, entry and storage

All data were double punched to ensure accuracy. Comprehensive validity and consistency checks were performed automatically to ensure data completeness and that data conformed to expected values and distributions. Requests for missing data and/or data queries were sent to collaborating centres on a monthly basis until resolution of the query. Records were then stored in secure filing cabinets. In addition, a monthly audit was performed on four records to compare paper copy with the computer copy (discharge and follow-up data) to ensure data accuracy further.

Interim analysis

The appointed DMC reviewed the results of an interim primary analysis on an annual basis. These data remained confidential to the DMC and Trial Statistician.

Stopping rules

If the DMC considered that the randomised comparisons provided both (1) 'proof beyond reasonable doubt' that one or both of the interventions were clearly indicated or clearly contraindicated and (2) evidence that might reasonably be expected to influence patient management materially in normal practice, then the trial could justifiably be stopped prematurely.

Appropriate criteria of 'proof beyond reasonable doubt' were not specified precisely, but some members of the DMC expressed sympathy with the view that a difference of at least three standard errors in an interim analysis of a major outcome event was an appropriate measure.

Prespecified subgroups

We planned to examine treatment effects on our primary outcomes subdivided by baseline nutritional status, baseline prognosis and time between stroke onset and randomisation for Trials 1 and 3. We also examined treatment effect by age at enrolment.

Statistical methods

The primary analyses were by intention-to-treat (ITT). The proportions of patients in each treatment arm with a dichotomous outcome (e.g. who were dead or had a poor outcome) were

compared with odds ratios (ORs) and 95% confidence intervals (CIs) derived from unadjusted logistic regression. Our primary prespecified analysis did not take account of any baseline imbalance. For death and in-hospital complications, Kaplan–Meier survival curves were constructed and the significance of any differences assessed with the log-rank test. Utilities derived from the EUROQoL were compared with the Wilcoxon 2 sample test. *p*-Values for subgroup analyses were calculated from the change in log-likelihood when the interaction between treatment and the subgroup of interest was entered into a logistic regression model.

Chapter 3

Trial conduct

The FOOD Trial was an international multicentre RCT which during its 8-year life-span developed many specific systems and services in order to maintain recruitment and optimise data quality. Changes in feeding practices were also monitored throughout this period. In this chapter we describe how the trial was actually conducted since inevitably the protocol was not adhered to in every aspect.

Adherence to legislation and guidelines

The FOOD Trial was an academic trial and complied, where appropriate, with the following guidelines/law which were introduced during the study period:

- The Data Protection Act 2000
- Good Clinical Practice
- Research Governance.

Accrual

Centres

To reach our target of 9000, an international collaborative effort was required. We sought collaboration from interested centres across the world via:

- mailshots to relevant professional networks (e.g. British Geriatric Society)
- presentations at professional meetings (poster and oral presentations)
- personal invitations to join
- requests to existing collaborators to identify their colleagues
- articles in relevant journals and newsletters with invitations to join.

As a result, 155 centres collaborated from countries world-wide following confirmation of the appropriate ethical approval. Of these centres, 24 (15%) from six countries did not randomise any patients into FOOD (*Table 3*), for a variety of reasons including closure of the hospital and departure of the key physician.

The majority of centres (86, 55%) were British, with Belgium, Brazil, Singapore and Hong Kong each having only one collaborating centre. The majority of centres (108, 70%) were recruited over the first three full years of the trial from 1997 to 1999 (*Table 3*).

Accrual of patients over time

A total of 5033 patients were recruited into the FOOD family of trials. Recruitment began on 18 November 1996. The pilot phase ended on 25 October 1998, after 754 patients had been randomised, and thereafter 4279 patients were randomised into the main phase from 26 October 1998 to 31 July 2003. We did not meet our planned sample size of 9000 (6000 into Trial 1, 2000 into Trial 2 and 1000 into Trial 3) (*Figure 6*).

Accrual of patients by trial and co-enrolment

Clinicians could, if they wished, co-enrol patients into more than one trial depending on their clinical uncertainty (see Chapter 2 for details). This increased the number of randomisations by 160 from 5033 to 5203. For three patients this involved randomisation into all three trials. A total of 4023 patients were recruited into Trial 1 from 125 centres. Of these, 90 (2%) were co-enrolled into more than one trial. A total of 859 patients were recruited into Trial 2 from 83 participating centres, of whom 149 (17%) were co-enrolled into more than one trial. A total of 321 patients were recruited into Trial 3 from 47 participating centres, of whom 98 (31%) were co-enrolled into more than one trial. Details of these co-enrolments and their timing are given with the main trial results in Chapter 4. Co-enrolment was used less often than we had originally hoped but it added significantly to the recruitment in Trials 2 and 3.

Randomisation

During the pilot phase of FOOD (18 November 1996 to 25 October 1998), the services of the Clinical Trials Services Unit (CTSU) were used to randomise patients into FOOD; thereafter a suite of in-house systems were used (see Chapter 2). Their usage is detailed in *Table 4*.

TABLE 3 *Accrual of centres over time*

Country	1996[a]	1997	1998	1999	2000	2001	2002	2003[b]	Total
UK	3	18 (1)[c]	28 (6)	15 (3)	11 (2)	4 (1)	6 (1)	1	86 (14)
Czech Republic		1	0	1	0	0	0		2
New Zealand		2	0	1	0	0	1 (1)		4 (1)
Canada		1	1	0	0	0	0		2
Poland		3 (1)	0	0	0	0	0		3 (1)
Italy		8 (3)	4 (1)	6	7	3 (1)	1		29 (5)
Australia		1	4	1	0	0	1		7
Belgium		1	0	0	0	0	0		1
Turkey		1	1	1	0	0	0		3
Portugal		1	0	1	3	1	0		6
Brazil		1	0	0	0	0	0		1
India			1	0	1	0	0		2
Singapore			1	0	0	0	0		1
Hong Kong				1	0	0	0		1
Republic of Ireland				1	0	1	0		2
Argentina				1 (1)	0	0	0		1 (1)
Denmark				1	2 (1)	1 (1)	0		4 (2)
Total	3	38 (5)	40 (7)	30 (4)	24 (3)	10 (3)	9 (2)	1	155 (24)

[a] First patient recruited 18 November 1996.
[b] Last patient recruited 31 July 2003.
[c] Figures in parentheses indicate the number of centres who did not randomise any patients.

TABLE 4 *Methods of randomisation*

Randomisation via	Total number of randomisations	% of total randomisations
CTSU	774	15
In-house randomisation service	4377	85
Total	5151	
Split by:		
Manual desktop service	2863	56
Automated service	1404	28
Italian language service	41 (of 609 Italian patients)	0.02 (10% of Italian patients)
FLIP/laptop	69	1

The majority of calls (56%) were taken by a member of the FOOD Trial team [consisting of the Trial Coordinator (40%), the computer programmer (19%) and four members of the data management staff (41%)]. The automated service was used in particular by those centres who were based several hours ahead of or behind Greenwich Mean Time and those who preferred to randomise outwith normal office hours. Where possible, a freephone telephone number was provided in order to randomise patients into FOOD (otherwise the costs of telephone calls were reimbursed if requested).

Surveys of practice and barriers to recruitment

In order to identify possible ways to increase recruitment, we conducted two surveys to establish the types of centres collaborating, their usual practice and feeding preferences. The first survey in 2000 received responses from 81 (94%) collaborating centres. The results of this survey revealed that many centres complied with policies relating to feeding which were not evidence based [e.g. 22/81 (27%) centres had policies relating to the initiation of tube feeding and 23/81 (28%) had

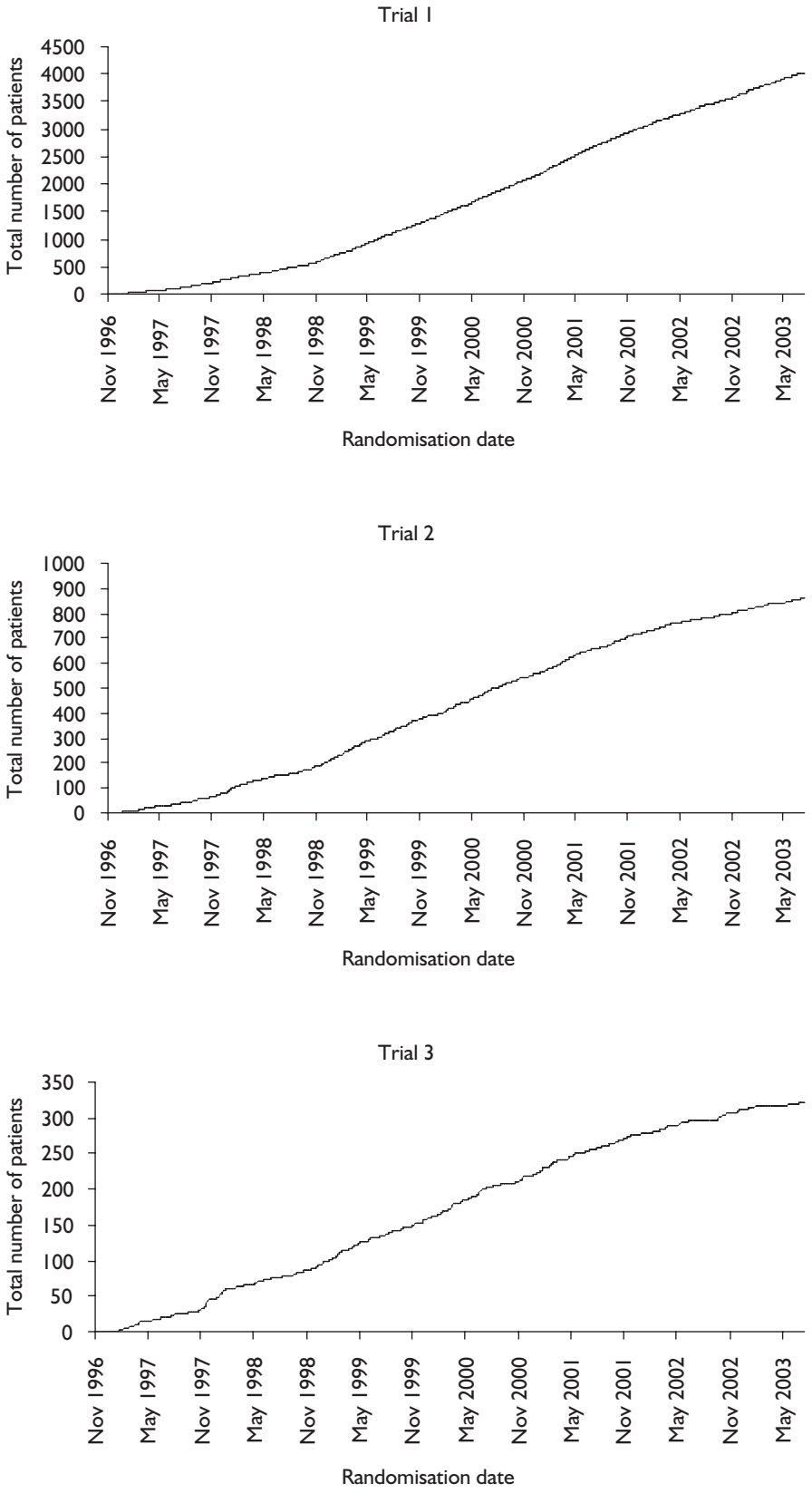

FIGURE 6 *Figure showing accrual over the study period in each of the three trials (targets were 6000, 2000 and 1000 in Trials 1, 2 and 3, respectively)*

TABLE 5 *Barriers to recruitment*

Lack of professional's time	• Provided some limited support (funded by the Stroke Association) to selected centres (e.g. a session of nurse's, dietitian's or speech therapist's time)
Lack of uncertainty	• Education regarding lack of evidence and the need for randomised trials • Encouraged the inclusion of statements to the effect that enrolment in relevant RCTs should be encouraged in relevant guidelines (e.g. RCP Guidelines)
Lack of access to prompt PEG tube insertion	• Encourage our coordinators to involve their gastroenterologists more closely.
Difficulties in obtaining consent	• Provided guidelines on obtaining consent • Introduced consent pictures to aid discussion
Lack of recognition for efforts in multicentre RCTs	• Prespecified publication policy outlined in the protocol which states that any papers are published in the name of the Collaboration and not an individual

policies relating to PEG feeding]. Half of the centres surveyed would not consider recruitment into FOOD Trial 3, stating that the 72-hour time window was not achievable.

The second survey was conducted in 2003. This involved not only FOOD collaborators but also all stroke physicians in the UK. This survey revealed that recruitment was hampered by the same issues raised by the first survey. However, in addition, a reluctance to recruit undernourished patients, to delay tube feeding for longer than 7 days and to insert a PEG tube without first trying an NG tube [99/121 (82%) said they would rarely or never do this] were also stated as barriers to recruitment. *Table 5* show the barriers to recruitment and some of the actions that we took to try to remove these. None were particularly successful. More details of the second survey (2003) are given in Chapter 7 since they are relevant when considering the implications of our trial results for practice in the UK.

Financial incentives

This trial did not receive any funds from industry. No 'per patient' payments were made to collaborating centres. The coordinating centre did not provide any feeding equipment or feeds to centres (apart from a one-off small supply of supplements to Centre 023 in Poland). The coordinating centre did provide centres with a Trial Manual that contained all the relevant paperwork which was required for the duration of the trial. Some UK centres, who were randomising significant numbers of patients, were provided with modest resources to help with enrolment and completion of discharge forms. In addition, recruitment drives were initiated in order to boost recruitment with the prize being modest (support to travel to a coordinators' meeting or a contribution to ward funds).

National coordinating centres (in Italy, Portugal, Turkey, New Zealand and Australia) were provided with expenses to cover the cost of telephone calls and/or postage of letters to patients in order to complete the 6-month follow-up.

Interim analyses and DMC reports

Prior to the start of recruitment, a four-member DMC was established (remit detailed in Chapter 2). On a yearly basis they met either in person or via teleconference to review the interim primary outcome data as provided by the Trial Statistician. During the course of the trial, five meetings were held and the recommendation was to continue to recruit after each.

Additional interim analyses were performed throughout the duration of the trial but these were not split by treatment. These analyses were required in order to encourage collaboration into FOOD and to provide existing collaborators with some results of interest.

Time and funding extensions

The trial received the bulk of its funding from the NHS R&D Health Technology Assessment (HTA)

Board. However, the start-up phase was supported by grants from the Stroke Association, Chief Scientist Office of the Scottish Executive and Chest, Heart and Stroke Scotland. In addition, the Stroke Association awarded a second grant to support the centres participating in the main phase of the trial. During the course of the trial, we have applied for two time-only extensions and one funding extension from the NHS R&D HTA board and a time-only extension to a Stroke Association grant:

1. An 11-month time-only extension from the NHS R&D HTA Board was agreed in 2002 to use up an under-spend which arose as a result of gaps in employment, utilisation of fewer consumables and savings on collaborators' meetings.

2. In 2002, additional funding was provided by the NHS R&D HTA Board to allow us to recruit a Recruitment Coordinator for a 1-year trial period. This post aimed to increase both the number of participating centres and to maximise recruitment in order to attempt to achieve our sample size. This person was specifically responsible for:
   (a) launching an intensive recruitment drive to identify more centres (especially those able to participate in Trials 2 and 3)
   (b) encouraging recruitment in existing centres
   (c) training staff
   (d) engaging gastroenterologists in order to involve them more closely and to facilitate earlier PEG insertion.

   In addition to funds to cover a Recruitment Coordinator, we also requested funds to cover a 9-month close-out period, which would ensure the completion of follow-ups, data cleanup and analyses.

   This person spent the majority of their time visiting centres, but she was unable to effect a significant increase in the rate of recruitment into FOOD.

3. A 4-month time-only extension to funding to 31 December 2004 was agreed in 2004.

The Stroke Association agreed to a time-only extension of its grant to cover the close-out period. They also agreed to their funding being used for purposes other than centre support – the original purpose of their grant.

Reasons for trial cessation

Although the DMC recommended continuation of recruitment into FOOD following their meeting in 2002, the Steering Committee took the decision to stop recruitment on 31 July 2003. This decision was based on the facts that (1) the survey of practice suggested that the rate of recruitment was unlikely to increase significantly owing to barriers which the trial was unable to overcome, hence the sample size was unlikely to be met, and (2) in order to ensure that adequate funds were set aside to complete the 6-month follow-up and data checking, recruitment would need to stop 12 months prior to the conclusion of funding.

Chapter 4
Results

In total, 5033 patients were recruited into the FOOD Trial. The start-up phase ran from 18 November 1996 to 25 October 1998, during which period 754 patients were randomised. Thereafter, 4279 patients were randomised into the main phase from 26 October 1998 to 31 July 2003. Patients from both phases were analysed together. Of the 5033 patients enrolled into the trials, 164 (3%) were co-enrolled into two of the trials and three into three trials (thus 5203 randomisations). A total of 131 centres randomised patients into the trials.

The results of each of the three trials are presented separately in the next three sections.

Trial 1: normal hospital diet versus normal hospital diet plus oral nutritional supplements

In total, 4023 patients were randomised into Trial 1 (2007 to NHD and 2016 to NHD+S).

Of these 4023 patients, 90 (2%) were co-enrolled into more than one trial. Sixty-nine patients were enrolled into Trials 1 and 2 only. All of these were enrolled into Trial 2 followed by Trial 1. The median time between enrolling in Trial 1 and enrolling in Trial 2 was 8 days [interquartile range (IQR) 6–12, minimum 1, maximum 24 days]. Eighteen patients were enrolled into Trials 1 and 3 only. Eight were enrolled into Trial 1 followed by Trial 3. The median time between enrolling in Trial 1 and enrolling in Trial 3 was 14 days (IQR 7–14, minimum 4, maximum 15 days). Ten were enrolled into Trial 3 followed by Trial 1. The median time between enrolling in Trial 3 and enrolling in Trial 1 was 13 days (IQR 7–20, minimum 3, maximum 27 days). Three patients were enrolled into Trials 1, 2 and 3. One was enrolled into Trial 2, then Trial 1 (5 days later), then Trial 3 (7 days later). Two were enrolled into Trials 2 and 3 concurrently, followed by Trial 1 (7 and 20 days later).

Data completeness

All 100% of baseline data were collected at randomisation; thereafter, 4015/4023 (99.8%) discharge forms and 4004/4023 (99.5%) follow-ups were received. For eight patients only vital status (i.e. dead or alive) was known at follow-up and 11/4023 (0.27%) patients were lost to follow-up (see flow diagram, *Figure* 7). Data on compliance, in-hospital complications and follow-up were collected for 9 months after enrolment was completed, until 31 March 2004, when the database was closed.

The follow-up data were collected in surviving patients a median of 6.7 months after enrolment (IQR 5.9–7.7). Of the 4004 follow-ups completed, 1406 (35%) forms were completed by the patient, 2029 (50.7%) by a spouse, relative, friend or carer, 59 (1.5%) by a doctor and was unknown in 16 (0.4%). The remaining 494 (12.3%) had died before follow-up.

Baseline data

The baseline data are given in *Table 6*. Patients were recruited into Trial 1 by 125 hospitals in 15 countries. The majority of patients were from the UK [2297 (57%)] with India and Italy contributing significant numbers [571 (14%) and 492 (12%), respectively]. The use of minimisation at randomisation ensured balance between treatment groups with respect to sex, age, nutritional status and predicted outcome. A total of 2149 (53%) were male with a mean age of 71 years in both treatment groups (range: 16–99 years). In all, 785 (20%) were <60 years old and 949 (24%) were >80 years old.

At baseline, the majority (3092, 77%) were considered normal weight, with 617 (15%) categorised as overweight and 314 (8%) underweight. Out of 1939 patients, 358 (18.5%) were diabetic (data for the remaining 2076 patients are unknown given that these data were only collected during the main phase of the trial). The method of nutritional assessment was collected after the first 482 patients had been enrolled and was available in only 3533 patients (see *Table* 7). In 2227 (63.0%), patients' nutritional status was assessed informally (i.e. based purely on simple observation). A total of 702 (19.9%) were weighed or had their body mass index (BMI) calculated, 487 (13.8%) were assessed by a dietitian, 381 (10.8%) had blood indices and 52 (1.5%) had anthropometric measurements taken.

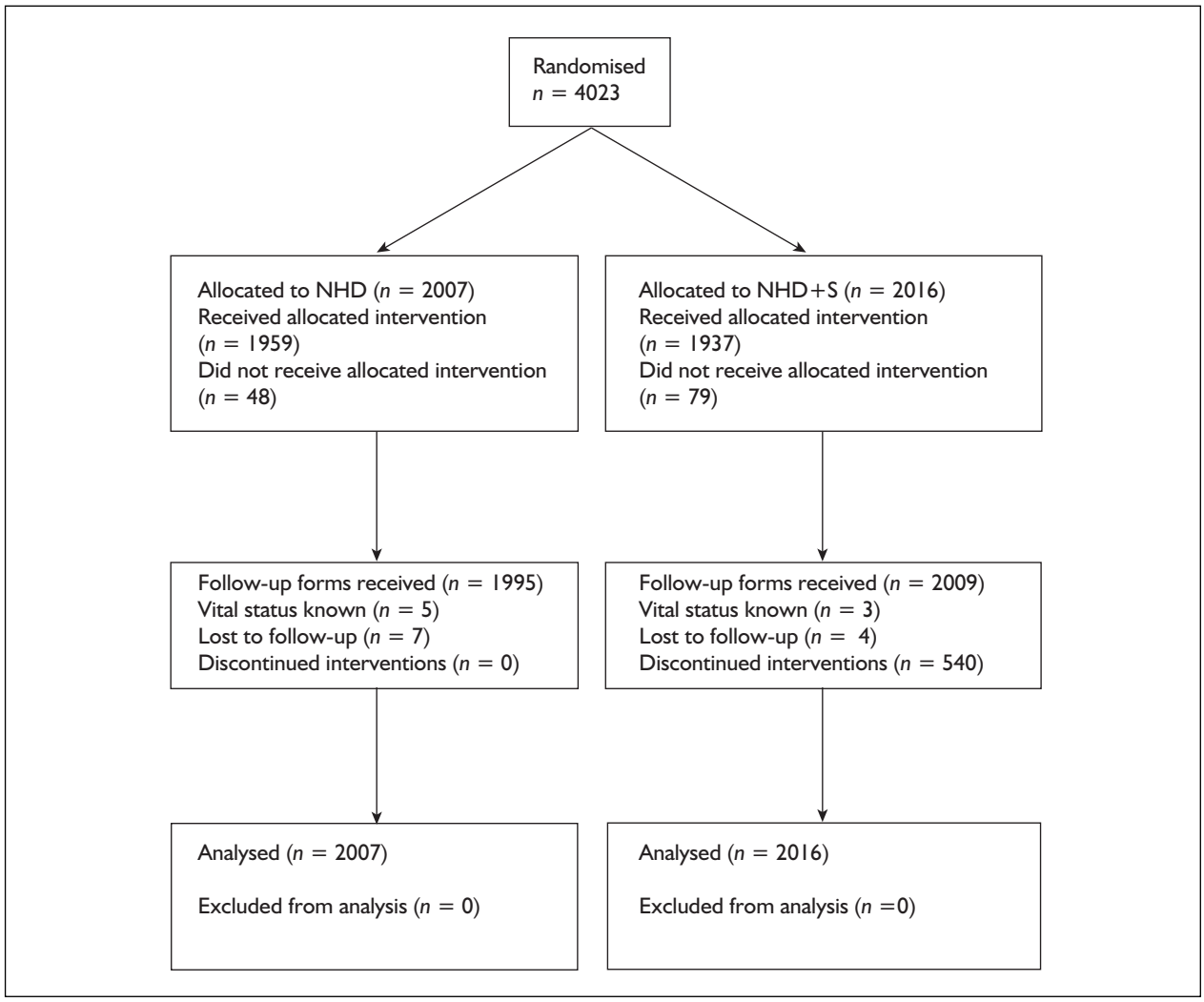

FIGURE 7 *CONSORT diagram for Trial 1*

As predicted, the majority of patients in Trial 1 had milder strokes because the trial excluded those with significant swallowing problems; 3250 (81%) were able to talk and orientated in time, place and person following their stroke, but only 920 (23%) could walk unaided.

Fifty-four (1.3%) patients were enrolled where the final diagnosis was other than stroke. The most common non-stroke diagnosis was cerebral tumour, in 22/54 cases (40%) (*Table 8*). These few patients were included in our primary analysis.

Most patients were admitted to hospital within 1 day of symptom onset (IQR 0–1) and were randomised a median of 5 days (IQR 3–9) after stroke onset.

Compliance with treatment allocation

Of the 2016 patients allocated supplements, 79 (3.9%) did not receive any, giving a crude compliance of 96.1%. The commonest reasons for non-compliance were staff error in 34 (43%), patient refusal in 15 (19%) and worsening clinical condition in six (8%). Of the 2007 patients allocated normal diet, 48 (2.4%) received some supplements, giving a crude compliance of 97.6%.

We calculated the percentage compliance for each patient. A patient was classed as 100% compliant if their period of supplementation equalled the duration of their hospital stay, with no missed doses recorded. *Figure 8* shows the distribution of compliance in the supplemented arm. The mean per-patient compliance was 75.5% with a median of 92.7%. The mean duration of hospital stay following enrolment was 34 days in the supplemented arm, so the average patient allocated supplements received about 14 litres of oral supplement. *Figure 9* shows the percentage of patients in each treatment arm who were receiving supplements in hospital, who were in hospital but

TABLE 6 *Baseline data in Trial 1*

		No supplements	Supplements	Total
Randomised		2007	2016	4023
Sex	Female	929 (46%)	945 (47%)	1874 (47%)
	Male	1078 (54%)	1071 (53%)	2149 (53%)
Age (years)	≤50	172 (9%)	147 (7%)	319 (8%)
	51–60	234 (12%)	232 (12%)	466 (12%)
	61–70	411 (20%)	447 (22%)	858 (21%)
	71–80	711 (35%)	720 (36%)	1431 (36%)
	>80	479 (24%)	470 (23%)	949 (24%)
Nutritional status	Underweight	158 (8%)	156 (8%)	314 (8%)
	Normal	1542 (77%)	1550 (77%)	3092 (77%)
	Obese	307 (15%)	310 (15%)	617 (15%)
Lived alone before admission	Yes	664 (33%)	649 (32%)	1313 (33%)
	No	1341 (67%)	1364 (68%)	2705 (67%)
	Unknown	2 (0.1%)	3 (0.2%)	5 (0.1%)
Independent in everyday activities before stroke	Yes	1847 (92%)	1838 (91%)	3685 (92%)
	No	159 (8%)	172 (9%)	331 (8%)
	Unknown	1 (0.05%)	6 (0.3%)	7 (0.2%)
Able to talk and orientated in time, place and person	Yes	1606 (80%)	1644 (82%)	3250 (81%)
	No	401 (20%)	372 (18%)	773 (19%)
Could lift both arms	Yes	1105 (55%)	1081 (54%)	2186 (54%)
	No	902 (45%)	935 (46%)	1837 (46%)
Could walk unaided	Yes	462 (23%)	458 (23%)	920 (23%)
	No	1545 (77%)	1558 (77%)	3103 (77%)
Diabetic	Yes	156 (16.3%)	202 (20.6%)	358 (18.5%)
	No	802 (83.7%)	779 (79.4%)	1581 (81.5%)
	Unknown	1049	1035	2084
Country	Australia	39 (2%)	40 (2%)	79 (2%)
	Belgium	0 (0%)	2 (0.1%)	2 (0.05%)
	Brazil	9 (0.5%)	9 (0.5%)	18 (0.5%)
	Canada	7 (0.4%)	7 (0.4%)	14 (0.4%)
	Czech Republic	7 (0.4%)	7 (0.4%)	14 (0.4%)
	Denmark	12 (0.6%)	12 (0.6%)	24 (0.6%)
	Hong Kong	5 (0.3%)	6 (0.3%)	11 (0.3%)
	India	286 (14%)	285 (14%)	571 (14%)
	Italy	246 (12%)	246 (12%)	492 (12%)
	New Zealand	154 (8%)	155 (8%)	309 (8%)
	Poland	3 (0.2%)	4 (0.2%)	7 (0.2%)
	Portugal	49 (2%)	48 (2%)	97 (2%)
	Republic of Ireland	5 (0.3%)	6 (0.3%)	11 (0.3%)
	Turkey	38 (2%)	39 (2%)	77 (2%)
	UK	1147 (57%)	1150 (57%)	2297 (57%)
Predicted probability of poor outcome (%)	<40	484 (24%)	493 (24%)	977 (24%)
	40–80	655 (33%)	636 (32%)	1291 (32%)
	80–90	292 (15%)	291 (14%)	583 (14%)
	90–95	226 (11%)	231 (11%)	457 (11%)
	>95	350 (17%)	365 (18%)	715 (18%)

not receiving supplements, who had been discharged or who had died during the first 6 months after randomisation. A total of 540 (27.9%) patients stopped receiving supplements before discharge. The predominant reason for stopping supplements prior to hospital discharge was patient refusal, owing to not liking the taste, unwanted weight gain or feeling nauseated. Poor glycaemic control led to premature stopping of supplements in 33 patients with diabetes mellitus.

TABLE 7 *Method of assessing nutritional status in Trial 1*[a]

		No supplements	Supplements	Total
Randomised		2007	2016	4023
No discharge form		6	2	8
Nutritional status not recorded (old form)		242	240	482
Data available		1759	1774	3533
Informal assessment	Yes	1482 (84.3%)	1485 (83.7%)	2967 (84.0%)
	No	276 (15.7%)	287 (16.2%)	563 (15.9%)
	Unknown	1 (0.06%)	2 (0.1%)	3 (0.08%)
Informal assessment only	*Yes*	*1105 (62.8%)*	*1122 (63.3%)*	*2227 (63.0%)*
	No	*653 (37.1%)*	*650 (36.6%)*	*1303 (36.9%)*
	Unknown	*1 (0.06%)*	*2 (0.1%)*	*3 (0.08%)*
Weight/BMI	Yes	359 (20.4%)	343 (19.3%)	702 (19.9%)
	No	1399 (79.5%)	1429 (80.6%)	2828 (80.1%)
	Unknown	1 (0.06%)	2 (0.1%)	3 (0.08%)
Dietitian's assessment	Yes	242 (13.8%)	245 (13.8%)	487 (13.8%)
	No	1516 (86.2%)	1527 (86.1%)	3043 (86.1%)
	Unknown	1 (0.06%)	2 (0.1%)	3 (0.08%)
Anthropometry	Yes	26 (1.5%)	26 (1.5%)	52 (1.5%)
	No	1732 (98.5%)	1746 (98.4%)	3478 (98.4%)
	Unknown	1 (0.06%)	2 (0.1%)	3 (0.08%)
Blood tests	Yes	192 (10.9%)	189 (10.7%)	381 (10.8%)
	No	1566 (89.0%)	1583 (89.2%)	3149 (89.1%)
	Unknown	1 (0.06%)	2 (0.1%)	3 (0.08%)
Other	Nutrition scoring	25 (1.4%)	31 (1.8%)	56 (1.6%)
	Other	1 (0.06%)	1 (0.06%)	2 (0.06%)
	Not done	1732 (98.5%)	1740 (98.1%)	3472 (98.3%)
	Unknown	1 (0.06%)	2 (0.1%)	3 (0.08%)

[a] Patients could be assessed using more than one method. The rows in italics indicate where a test was used alone (and no other tests were done). All other rows show the numbers of patients who were assessed using a method either alone or in combination with other methods.

TABLE 8 *Non-stroke diagnoses in Trial 1*

	No supplements	Supplements	Total
Randomised	2007	2016	4023
No discharge form	6	2	8
Data available	2001	2014	4015
Diagnosis			
Stroke	1976 (98.8%)	1985 (98.6%)	3961 (98.7%)
Not stroke	25 (1.3%)	29 (1.4%)	54 (1.3%)
Cerebral tumour	11	11	22
Functional	4	3	7
Worsening of previous stroke	0	4	4
Dementia	1	2	3
Subarachnoid haemorrhage	0	2	2
Multiple sclerosis	1	0	1
Seizure/fit/epilepsy	0	3	3
Transient ischaemic attack	3	1	4
Other	5	3	8

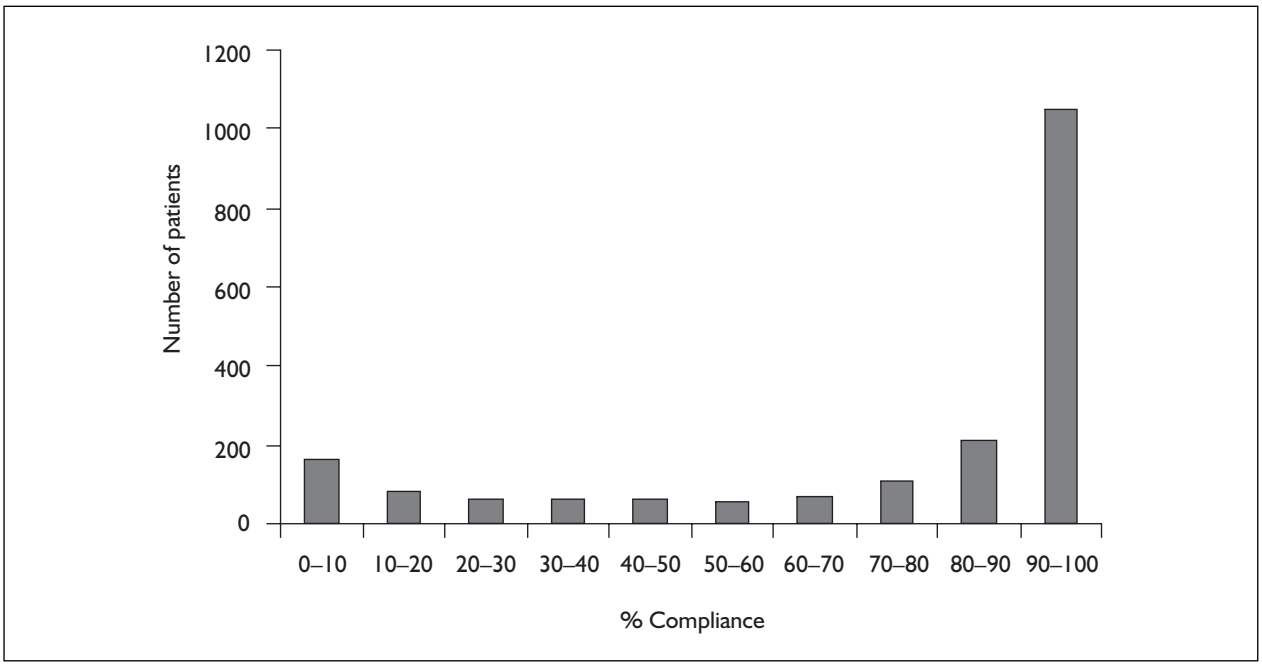

FIGURE 8 *Distribution of compliance with supplements in the NHD+S arm. These data were available for 1922 (95%) patients. A patient was classed as 100% compliant if their period of supplementation equalled the duration of their hospital stay, with no missed doses recorded.*

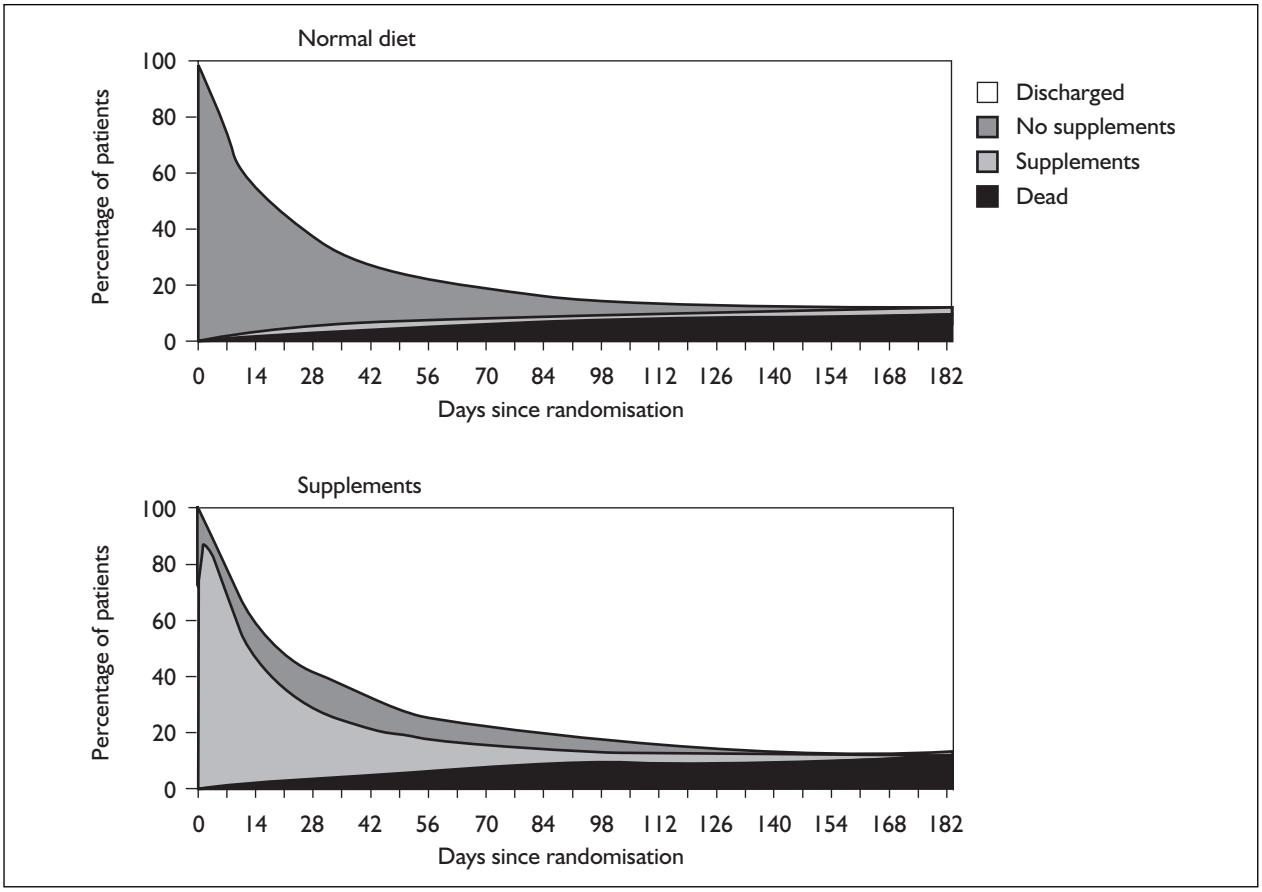

FIGURE 9 *Percentage of patients receiving oral supplements or not receiving supplements after enrolment during hospital admission, the percentage who were discharged and the percentage who had died in the two treatment groups during the first 6 months after randomisation in Trial 1. These data were not available for 8 (0.2%) patients. No information was available about use of oral supplements after discharge.*

TABLE 9 *Causes of death in Trial 1*

	No supplements	Supplements	Total
Initial stroke	40 (15.8%)	25 (10.4%)	65 (13.2%)
Pneumonia	57 (22.5%)	73 (30.3%)	130 (26.3%)
Pulmonary embolism	8 (3.2%)	13 (5.4%)	21 (4.3%)
Recurrent stroke	43 (17.0%)	39 (16.2%)	82 (16.6%)
Coronary heart disease	29 (11.5%)	27 (11.2%)	56 (11.3%)
Other vascular	19 (7.5%)	25 (10.4%)	44 (8.9%)
Sudden death	6	8	14
GI haemorrhage	0	3	3
Cardiac failure	6	3	9
Peripheral	4	8	12
Other	2	0	2
Uncertain cause	1	3	4
Other non-vascular	54 (21.3%)	39 (16.2%)	93 (18.8%)
Carcinoma	20	12	32
Suicide	2	0	2
Old age (on death certificate)	1	2	3
Respiratory failure	11	3	14
Sepsis	8	9	17
Dementia	3	0	3
Renal failure	4	7	11
Earthquake/trauma	2	1	3
Other	2	4	6
Uncertain cause	1	1	2
Missing	3 (1.1%)	0 (0%)	3 (0.6%)
Total	253	241	494

GI, gastrointestinal.

Adverse events

No serious life-threatening adverse effects of allocated treatment were reported. However, one patient experienced three petit mal fits, which were thought to be caused by the oral supplement inhibiting absorption of phenytoin.

Causes of death

None of the 494 deaths in this trial were attributed to the trial treatment by the investigators. There were 12 fewer deaths in the supplement arm of the trial but the difference was not clearly attributable to any single cause. The most common cause of death was pneumonia (130, 26.3%). *Table 9* presents these data.

Primary outcome

The sample size calculations were based on a dichotomous outcome – death or poor outcome (MRS 3–5) at follow-up. The two primary analyses are based on death or poor outcome and overall survival, subdivided by allocated treatment, irrespective of compliance.

The numbers and proportion of enrolled patients who died and the MRS of survivors in each treatment arm are given in *Table 10* (and graphically in *Figures 10* and *11*). Allocation to a supplemented diet was associated with an OR of 0.94 (95% CI 0.78 to 1.13) for death and 1.03 (95% CI 0.91 to 1.17) for death or poor outcome. The absolute difference in the risk of death was 0.7% (95% CI –1.4 to 2.7) in favour of the supplemented diet, but was 0.7% (95% CI –2.3 to 3.8) in favour of normal diet with respect to death or poor outcome (*Figure 12*). There was no significant difference between the Kaplan–Meier survival curves (log-rank test, $p = 0.7$; *Figure 13*).

Our primary analyses were not adjusted for any baseline imbalance in factors used in our minimisation routine. The effects on our two primary outcomes of adjusting for these variables are shown in *Table 11*.

Secondary outcomes

In-hospital complications

Pneumonia and urinary infections were the commonest reported complications [246/4015 (6.1%) and 276/4015 (6.9%), respectively; *Table 12*). The number of patients with reported pressure sores was 26/2001 (1.3%) in those allocated normal diet and 15/2014 (0.7%) in those allocated supplements ($p = 0.05$). There were

TABLE 10 *Number and proportion of patients with each MRS score, primary outcome and death by treatment allocation in Trial 1*

MRS score	No supplements (*n* = 2007)	Supplements (*n* = 2016)	Risk difference (95% CI)
0	159 (7.9%)	164 (8.1%)	
1	313 (15.6%)	308 (15.3%)	
2	352 (17.5%)	343 (17.0%)	
3	456 (22.7%)	507 (25.1%)	
4	242 (12.1%)	228 (11.3%)	
5	220 (11.0%)	218 (10.8%)	
Dead	253 (12.6%)	241 (12.0%)	–0.7 (–2.7 to 1.4)
Alive but MRS not known	5 (0.2%)	3 (0.1%)	
Outcome not known	7 (0.3%)	4 (0.2%)	
MRS 3–5	918 (45.7%)	953 (47.3%)	
Death or MRS 3–5	1171 (58.3%)	1194 (59.2%)	0.7 (–2.3 to 3.8)
Total	2007	2016	

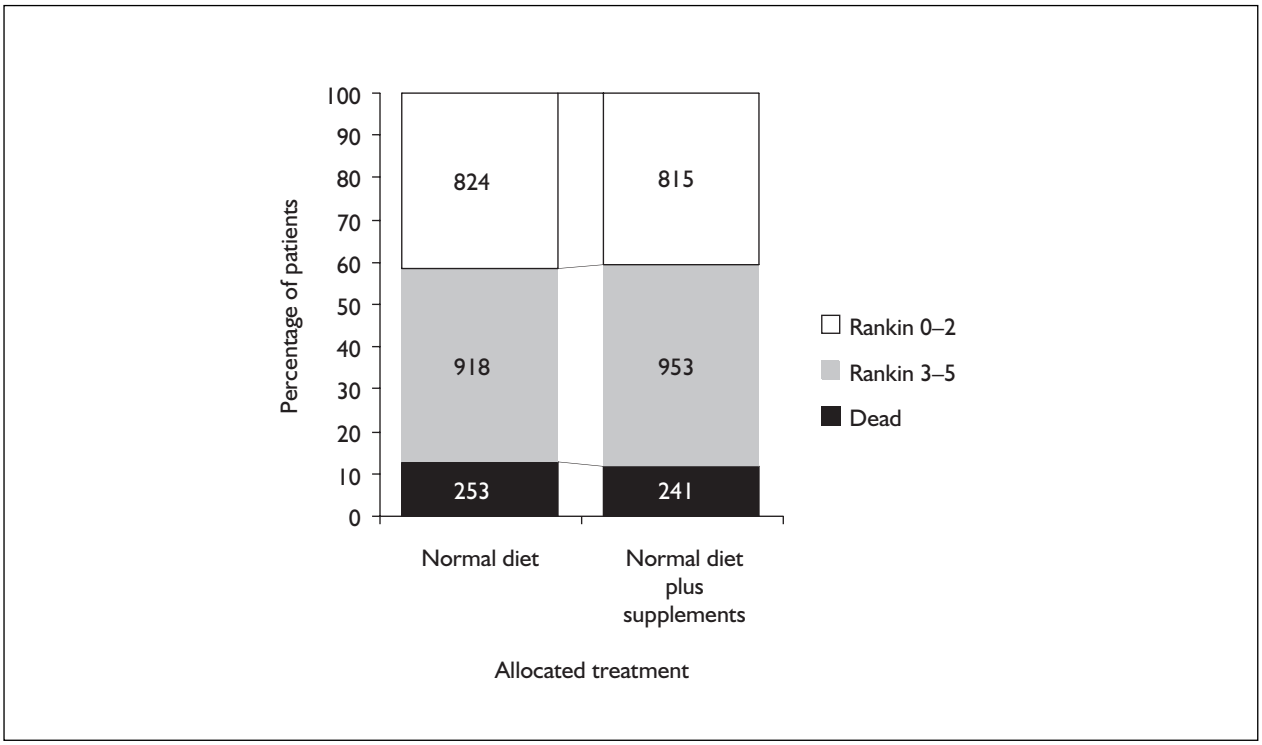

FIGURE 10 *Proportion of patients with primary outcomes according to treatment allocation and the absolute differences between treatment groups in Trial 1. Patients with missing outcomes have been omitted as there are too few to show up.*

TABLE 11 *Effect on primary outcomes of adjusting for baseline imbalance in minimisation factors between treatment groups in Trial 1*

Outcome		OR	95% CI	*p*-Value
Dead or MRS 3–5	Unadjusted	1.031	0.91 to 1.17	0.636
	Adjusted[a]	1.045	0.91 to 1.20	0.536
Dead	Unadjusted	0.940	0.78 to 1.13	0.517
	Adjusted[a]	0.944	0.78 to 1.15	0.562

[a] Adjusted analyses have been adjusted for variables from the minimisation algorithm: country (Italy, India, New Zealand, UK, other), age (<75, >75 years), sex, probability of poor outcome (<0.35, >0.35) and nutritional status (normal, undernourished, overweight).

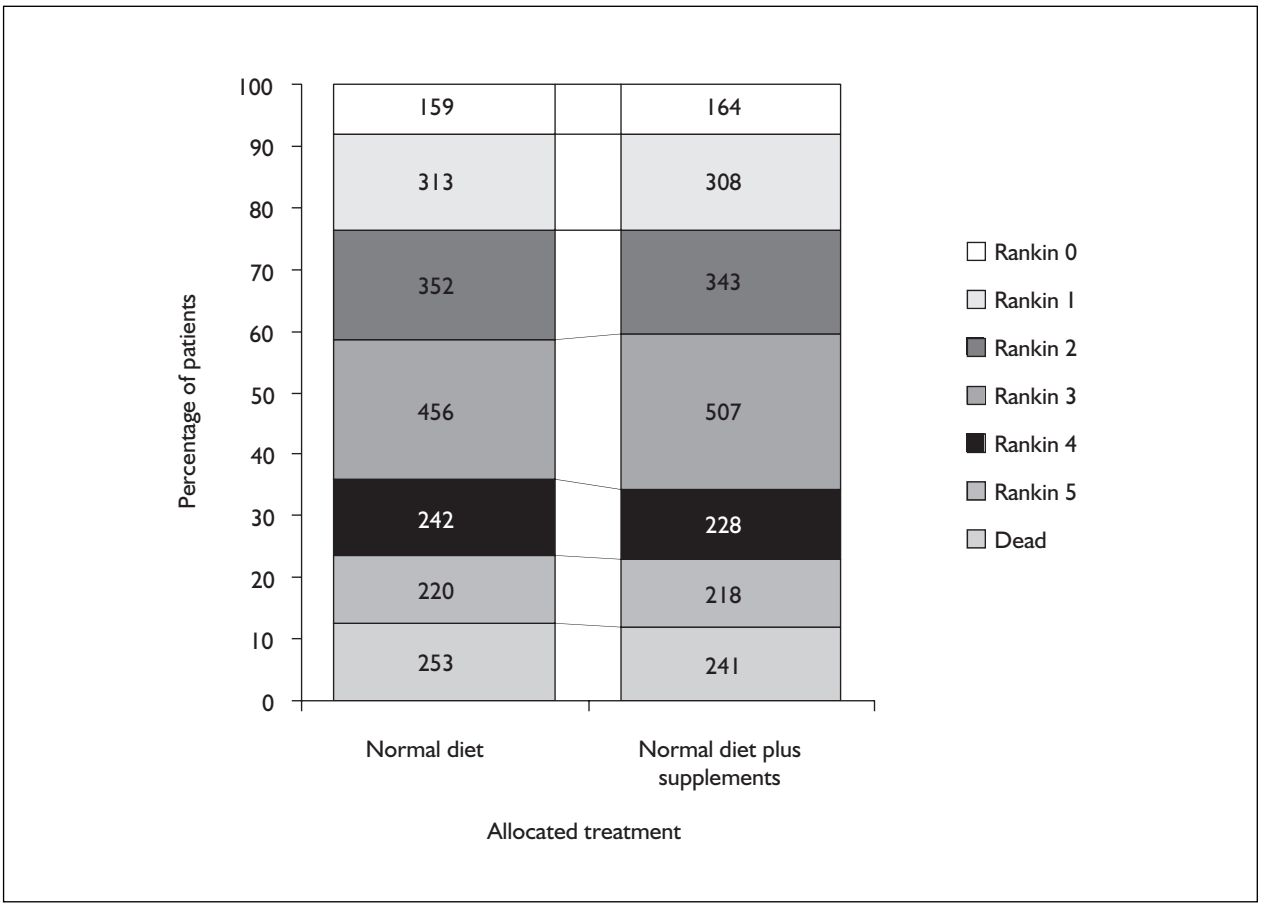

FIGURE 11 *Number and proportion of patients with each MRS score, primary outcome and death by treatment allocation in Trial 1*

Outcome	Supplements *n*/*N* (%)	No supplements *n*/*N* (%)	Risk difference (95% CI)	*p*-Value
Modified Rankin 3–6 versus 0–2	1194/2009 (59.4%)	1171/1995 (58.7%)	0.007 (–0.023 to +0.038)	0.636
Death	241/2012 (12.0%)	253/2000 (12.7%)	–0.007 (–0.027 to +0.014)	0.517

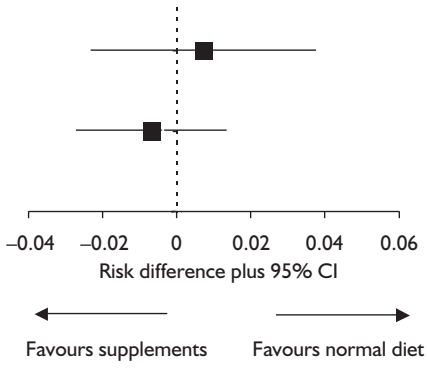

FIGURE 12 *Risk ratios comparing the primary outcomes of the two treatment groups in Trial 1*

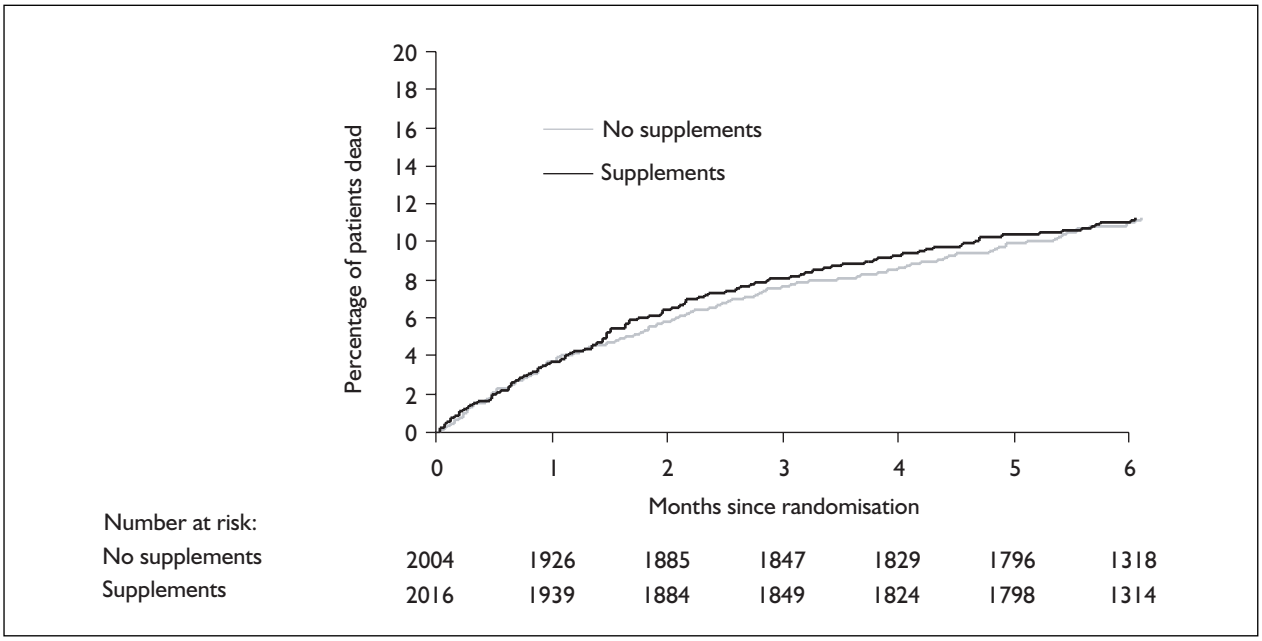

FIGURE 13 *Kaplan–Meier survival curves for the two treatment groups in Trial 1*

differences in the rates of diarrhoea and glycaemic control, but these data on complications need to be interpreted with caution because we could not blind this evaluation to allocated treatment and it was not feasible to have local source data verified for the occurrence of these.

Length of hospital stay and discharge destination

LOS (from randomisation to discharge) was available for 2001/2007 (99.7%) in the NHD group and 2011/2016 (99.8%) in the NHD+S group. The median LOS was 16 days in both groups [normal diet, IQR 7–41, mean 32, standard deviation (SD) 45; supplemented group, IQR 7–44, mean 34, SD 48]. The difference in mean lengths of stay (normal diet – supplemented) was –2.1 days (95% CI –5.0 to +0.8). Over half of all patients (2244/4023, 55.8%) were discharged home with a partner or relative whereas 690 (17.2%) were discharged home alone [compared with 1313 (33%) who lived alone prior to their stroke]. There were no significant differences in the discharge destinations between the two groups (*Table 13*). *Table 14* shows the place of residence at final follow-up. Again there were no major differences, or statistically significant differences between the treatment groups.

Quality of life (EuroQol)

QoL data were available in 3986/4023 (99.1%) patients. *Table 15* shows the categorisation of patients in each treatment group according to the five domains covered by the EuroQol. No differences were observed between the treatment groups in terms of mobility, self-care, usual activities, pain/discomfort and anxiety/depression.

Figure 14 shows the distribution of utilities derived from these responses for patients allocated each treatment. The median utility for all patients including those who died was 0.52 (IQR 0.03–0.74) in both treatment groups ($p > 0.9$) [difference of means (NHD – NHD+S) = +0.001 (95% CI –0.023 to +0.025)]. Patients who died were allocated a utility of zero. If patients who had died were excluded the median utility was 0.59 (IQR 0.19–0.80).

Subgroup analyses

The primary outcomes of patients subdivided by age, baseline nutritional status, tertiles of predicted stroke outcome and time between stroke onset and randomisation (early randomisation is <7 days post-stroke onset) are shown in *Figure 15*. There was no statistically significant heterogeneity between any subgroups or either of our primary outcomes. There was a non-significant difference in the point estimates for death or MRS 3–5, indicating that undernourished patients may benefit from supplements (OR 0.785, 95% CI 0.46 to 1.35) and obese patients may not (in line with one of our *a priori* hypotheses), but the CIs around these estimates were very wide (OR 1.201, 95% CI 0.87 to 1.65). Although deaths among undernourished patients were fewer in the supplemented group (OR 0.87, 95% CI 0.54 to 1.42), they were also fewer among obese patients.

TABLE 12 *Secondary outcomes – in-hospital complications in Trial 1*

Outcome		No supplements	Supplements	Total	Log-rank *p*-Value
Randomised		2007	2016	4023	
No discharge form		6	2	8	
Data available		2001	2014	4015	
Recurrent stroke	Yes	43 (2.2%)	50 (2.5%)	93 (2.3%)	
	No	1958 (97.9%)	1964 (97.5%)	3922 (97.7%)	0.59
Neurological worsening	Yes	51 (2.6%)	53 (2.6%)	104 (2.6%)	
	No	1949 (97.4%)	1961 (97.4%)	3910 (97.4%)	0.96
	Yes but date unknown	1 (0.05%)	0 (0%)	1 (0.02%)	
Pneumonia	Yes	116 (5.8%)	130 (6.5%)	246 (6.1%)	
	No	1885 (94.2%)	1883 (93.5%)	3768 (93.9%)	0.58
	Yes but date unknown	0 (0%)	1 (0.05%)	1 (0.02%)	
Pulmonary embolism	Yes	18 (0.9%)	23 (1.1%)	41 (1.0%)	
	No	1983 (99.1%)	1991 (98.9%)	3974 (99.0%)	0.51
Deep-vein thrombosis	Yes	29 (1.5%)	43 (2.1%)	72 (1.8%)	
	No	1972 (98.6%)	1971 (97.9%)	3943 (98.2%)	0.13
Pressure sores	Yes	26 (1.3%)	15 (0.7%)	41 (1.0%)	
	No	1975 (98.7%)	1999 (99.3%)	3974 (99.0%)	0.0507
GI haemorrhage	Yes	18 (0.9%)	28 (1.4%)	46 (1.2%)	
	No	1983 (99.1%)	1986 (98.6%)	3969 (98.9%)	0.18
UTI/cystitis including MRSA	Yes	143 (7.2%)	133 (6.6%)	276 (6.9%)	
	No	1858 (92.9%)	1881 (93.4%)	3739 (93.1%)	0.34
Skin conditions	Yes	22 (1.1%)	20 (1.0%)	42 (1.1%)	
	No	1978 (98.9%)	1994 (99.0%)	3972 (98.9%)	0.67
	Yes but date unknown	1 (0.05%)	0 (0%)	1 (0.02%)	
Other infections[a]	Yes	57 (2.9%)	39 (1.9%)	96 (2.4%)	
	No	1943 (97.1%)	1974 (98.0%)	3917 (97.6%)	0.0303
	Yes but date unknown	1 (0.05%)	1 (0.05%)	2 (0.05%)	
Diarrhoea	Yes	7 (0.4%)	12 (0.6%)	19 (0.5%)	
	Yes but date unknown	1 (0.05%)	22 (1.1%)	23 (0.6%)	<0.0001[c]
	No	1993 (99.6%)	1980 (98.3%)	3973 (99.0%)	
Hyper/hypoglycaemia	Yes	3 (0.2%)	27 (1.3%)	30 (0.8%)	
	Yes but date unknown	0 (0%)	19 (0.9%)	19 (0.5%)	<0.0001[c]
	No	1998 (99.9%)	1968 (97.7%)	3966 (98.8%)	
Acute coronary/cardiac arrest	Yes	22 (1.1%)	28 (1.4%)	50 (1.3%)	
	No	1979 (98.9%)	1986 (98.6%)	3965 (98.8%)	0.48
Other medical complications[b]	Yes	127 (6.4%)	118 (5.9%)	245 (6.1%)	
	No	1873 (93.6%)	1896 (94.1%)	3769 (93.9%)	0.34
	Yes but date unknown	1 (0.05%)	0 (0%)	1 (0.02%)	

MRSA, methicillin-resistant *Staphylococcus aureus*; UTI, urinary tract infection.

[a] 'Other' includes all categories of infections that were experienced by <1% of patients [including infections of eye, mouth, bile, Venflon/subcut site, PEG site (including MRSA)], MRSA infections, *C. difficil*e infections, infections of known origin, infections of unknown origin, other infections].

[b] 'Other' includes all categories of other medical complications that were experienced by <1% of patients (including MRSA colonisation, haemorrhage, neurological condition, electrolyte disturbance, renal/urinary problems, skeleton/joint/trauma, carcinoma, lung/respiratory, gastric/bowel, anaemia, gout, fracture, benign tumour, psychiatric, peripheral vascular disease, cardiac failure, cardiac rhythm disturbance, epistaxis).

[c] These are from a Fisher's exact test. These were too many missing data to use a log-rank test.

TABLE 13 *Place discharged to in Trial 1*

	No supplements	Supplements	Total
Randomised	2007	2016	4023
Own home alone	347 (17.3%)	343 (17.0%)	690 (17.2%)
At home, with partner/relative	1121 (55.9%)	1123 (55.7%)	2244 (55.8%)
Relative's home	47 (2.3%)	46 (2.3%)	93 (2.3%)
Residential home	73 (3.6%)	60 (3.0%)	133 (3.3%)
Nursing home	112 (5.6%)	122 (6.1%)	234 (5.8%)
Other hospital	132 (6.6%)	140 (6.9%)	272 (6.8%)
Other	61 (3.0%)	73 (3.6%)	134
Specialist ward	11	7	8
Rehabilitation/nursing home	33	51	84
Own home/sheltered housing	17	14	31
Other	0	1	1
Not discharged from hospital	0 (0%)	2 (0.1%)	2 (0.05%)
Dead	108 (5.4%)	105 (5.2%)	213 (5.3%)
No discharge form	6 (0.3%)	2 (0.1%)	8 (0.2%)

TABLE 14 *Residence at follow-up in Trial 1*

Residence	No supplements	Supplements	Total
Randomised	2007	2016	4023
Own home alone	353 (17.6%)	378 (18.8%)	731 (18.1%)
Own/relative's home with partner/relative	1111 (55.4%)	1124 (55.6%)	2235 (55.6%)
Residential home	98 (4.9%)	84 (4.2%)	182 (4.5%)
Nursing home	138 (6.9%)	133 (6.6%)	271 (6.7%)
Alive, not in hospital, but otherwise unknown	0 (0%)	1 (0.05%)	1 (0.02%)
Hospital	42 (2.1%)	48 (2.4%)	90 (2.2%)
Dead	253 (12.6%)	241 (12.0%)	494 (12.3%)
No follow-up	12 (0.6%)	7 (0.4%)	19 (0.5%)

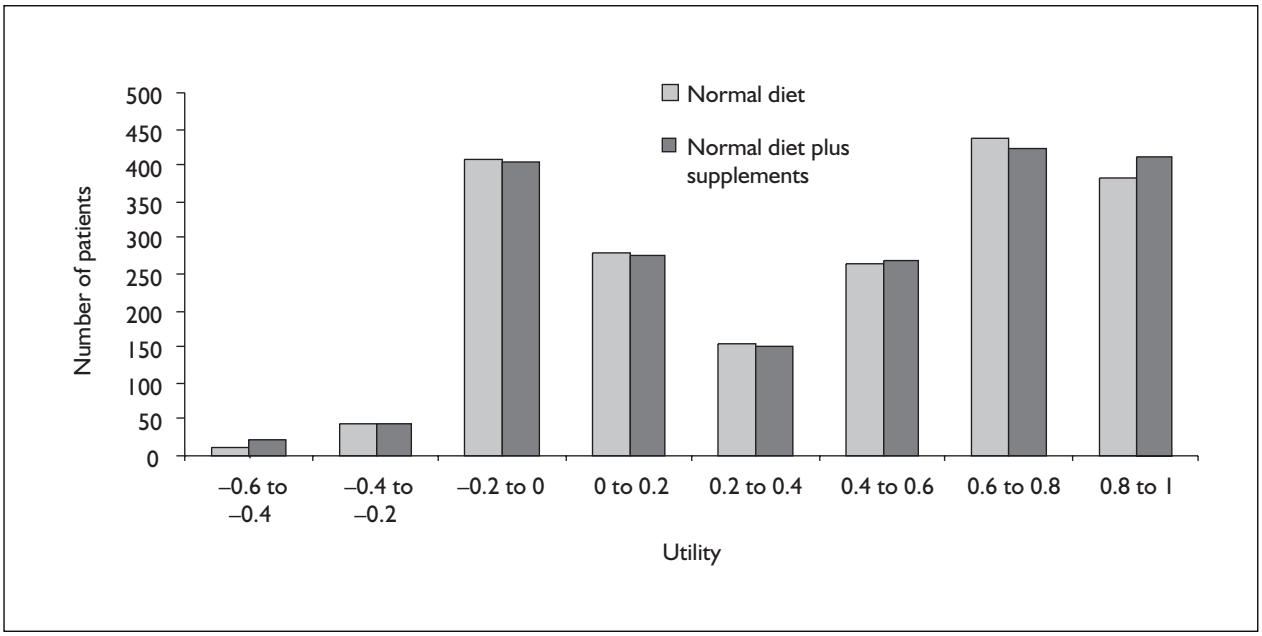

FIGURE 14 *Distribution of utilities (based on EuroQol) for the two treatment groups in Trial 1*

TABLE 15 *Quality of life (EUROQoL) at final follow-up in Trial 1*

	No supplements	Supplements	Total
Randomised	2007	2016	4023
Mobility			
No problems	545 (27.2%)	499 (24.8%)	1044 (26.0%)
Some problems	1048 (52.2%)	1101 (54.6%)	2149 (53.4%)
Confined to bed	147 (7.3%)	167 (8.3%)	314 (7.8%)
Alive, data unknown	2 (0.1%)	1 (0.05%)	3 (0.07%)
Dead	253 (12.6%)	241 (12.0%)	494 (12.3%)
No follow-up	12 (0.6%)	7 (0.4%)	19 (0.5%)
Self-care			
No problems	727 (36.2%)	752 (37.3%)	1479 (36.8%)
Some problems	717 (35.7%)	671 (33.3%)	1388 (34.5%)
Unable	294 (14.7%)	343 (17.0%)	637 (15.8%)
Alive, data unknown	4 (0.2%)	2 (0.1%)	6 (0.2%)
Dead	253 (12.6%)	241 (12.0%)	494 (12.3%)
No follow-up	12 (0.6%)	7 (0.4%)	19 (0.5%)
Usual activities			
No problems	403 (20.1%)	409 (20.3%)	812 (20.2%)
Some problems	794 (39.6%)	789 (39.1%)	1583 (39.4%)
Unable	542 (27.0%)	569 (28.2%)	1111 (27.6%)
Alive, data unknown	3 (0.2%)	1 (0.05%)	4 (0.1%)
Dead	253 (12.6%)	241 (12.0%)	494 (12.3%)
No follow-up	12 (0.6%)	7 (0.4%)	19 (0.5%)
Pain/discomfort			
None	700 (34.9%)	719 (35.3%)	1419 (35.3%)
Moderate	930 (46.3%)	937 (46.4%)	1867 (46.4%)
Extreme	107 (5.3%)	106 (5.3%)	213 (5.3%)
Alive, data unknown	5 (0.3%)	6 (0.3%)	11 (0.3%)
Dead	253 (12.6%)	241 (12.0%)	494 (12.3%)
No follow-up	12 (0.6%)	7 (0.4%)	19 (0.5%)
Anxiety/depression			
None	777 (38.7%)	807 (40.0%)	1584 (39.4%)
Moderate	820 (40.9%)	802 (39.8%)	1622 (40.3%)
Extreme	138 (6.9%)	153 (7.6%)	291 (7.2%)
Alive, data unknown	7 (0.4%)	6 (0.3%)	13 (0.3%)
Dead	253 (12.6%)	241 (12.0%)	494 (12.3%)
No follow-up	12 (0.6%)	7 (0.4%)	19 (0.5%)

Trial 2: early enteral tube feeding versus avoid enteral tube feeding

A total 859 patients were recruited into Trial 2, of whom 175 were randomised during the start-up phase (from 20 November 1996 to 25 October 1998). The remaining 684 patients were randomised during the main phase of the trial from 26 October 1998 to 17 July 2003.

Of the 859 patients enrolled into the trials, 149 (17%) were co-enrolled into more than one trial. Sixty-nine patients were enrolled into Trials 1 and 2 only. All were enrolled into Trial 2 followed by Trial 1. The median time between enrolling in Trial 1 and enrolling in Trial 2 was 8 days (IQR 6–12, minimum 1, maximum 24 days).

Seventy-seven patients were enrolled into Trials 2 and 3 only. Twenty-seven were enrolled into Trial 2 followed by Trial 3. The median time between enrolling in Trial 2 and enrolling in Trial 3 was 9 days (IQR 7–11, minimum 5, maximum 22 days). Ten were allocated avoid tube and then NG, 12 avoid tube and then PEG, two early NG and three early PEG. Fifty were enrolled into Trials 2 and 3 concurrently. Twenty-five were allocated early NG and 25 early PEG. Three patients were enrolled

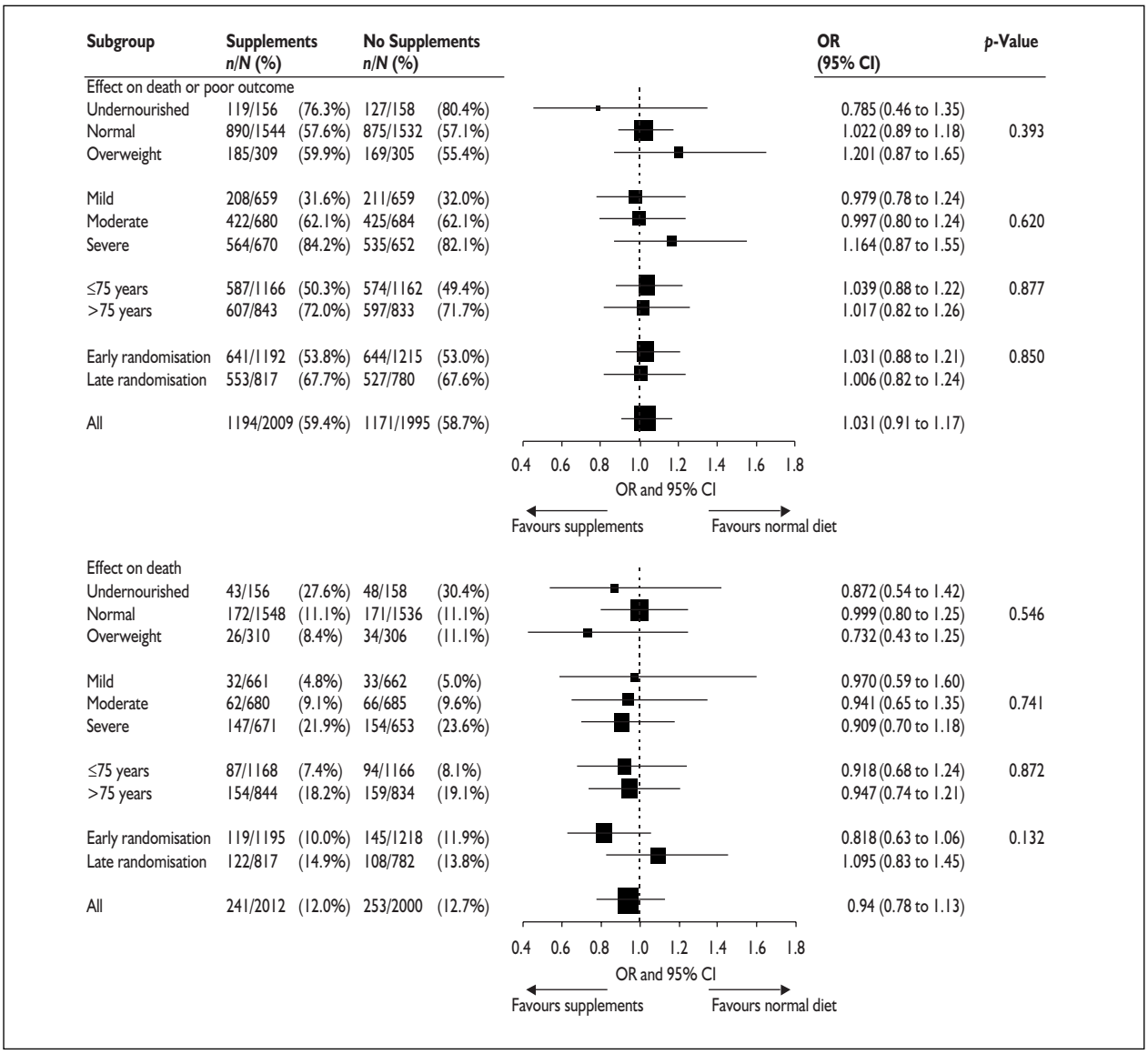

FIGURE 15 *Prespecified subgroup analysis. Secondary effect of oral supplements (a) death or poor outcome and (b) death subdivided by baseline nutritional status, stroke severity defined by tertiles of predicted risk of poor outcome, age and delay from stroke to randomisation. Results are expressed as OR and 95% CI.*

into Trials 1, 2 and 3. One was enrolled into Trial 2, then Trial 1 (5 days later), then Trial 3 (7 days later). This patient was allocated avoid tube in Trial 2 and PEG in Trial 3. Two were enrolled into Trials 2 and 3 concurrently, followed by Trial 1 (7 and 20 days later). These patients were both allocated early tube in Trial 2, but one was allocated NG and one PEG in Trial 3.

Data completeness

In total, 859 patients were randomised into Trial 2 (430 to avoid tube feeding for 1 week and 429 to early tube feeding). All 100% of baseline data were collected at randomisation; thereafter, 857/859 (99.8%) discharge forms and 858/859 (99.9%) follow-ups were received. In two cases, discharge forms were not available, but both patients died. One patient was lost to follow-up (see CONSORT diagram, *Figure 16*). Data on compliance, in-hospital complications and follow-up were collected until 5 April 2004, when the database was closed.

The follow-up data were collected in surviving patients a median of 6.5 months (IQR 5.8–7.8) after randomisation in the avoid tube group compared with 6.8 months (IQR 6.0–8.3) in the early tube group (Wilcoxon test, $p = 0.06$). Of the

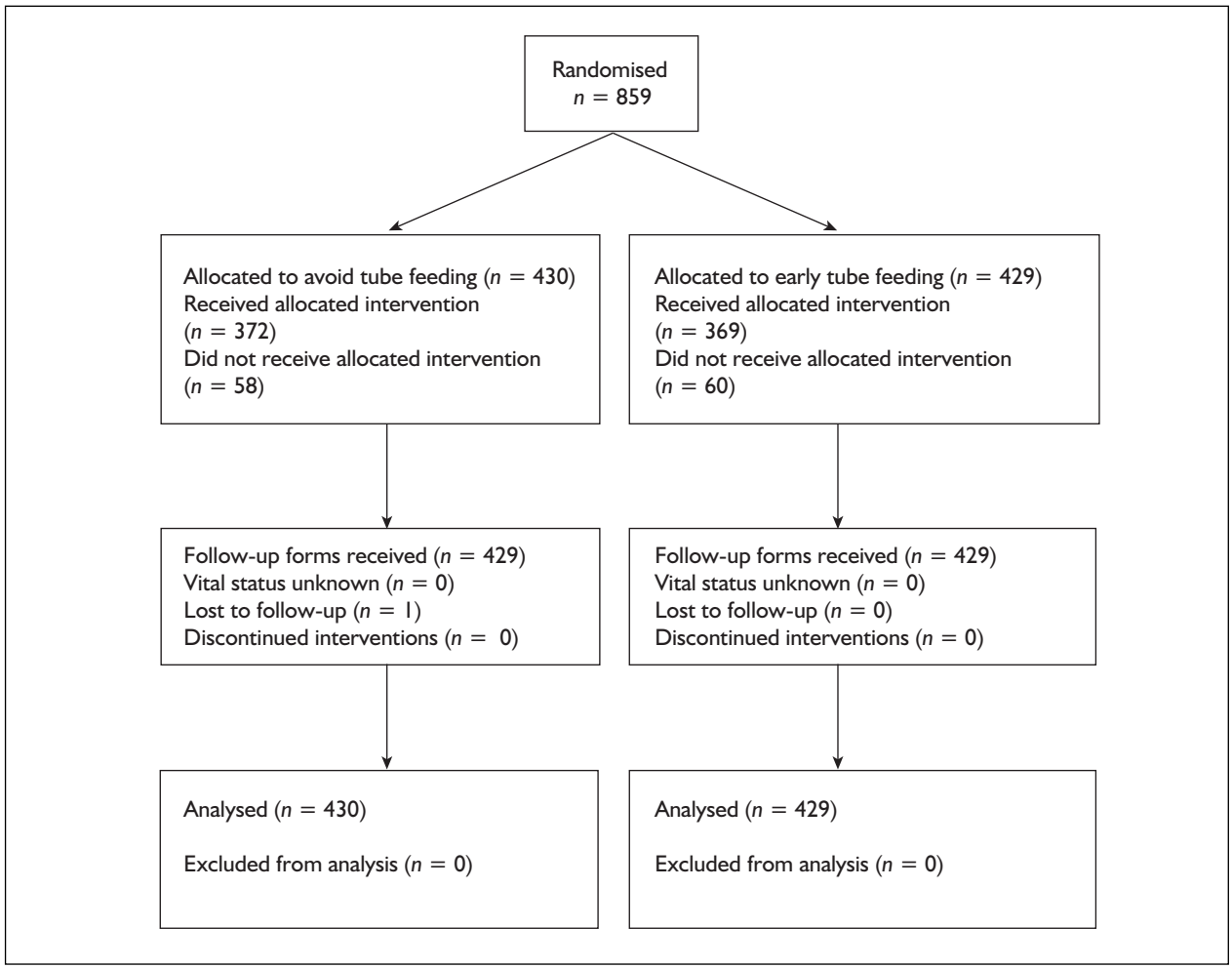

FIGURE 16 *CONSORT diagram for Trial 2*

858 follow-ups completed, 389 (45.3%) patients had died and the forms were completed by a spouse, relative, friend or carer in 379 (44.2%), by the patient in only 72 (8.4%), by a doctor in 17 (2.0%) and by an unknown person in one (0.1%).

Baseline data

Table 16 shows the baseline data. Eighty-three centres in 15 countries randomised patients into this trial. The majority of patients were from the UK (468, 54%). The use of minimisation at randomisation ensured balance between treatment group with respect to sex, age, nutritional status and predicted outcome. A total of 394 (46%) were male with a mean age of 76 years (SD 11) in both groups (range: 25–98 years). Eighty-eight (11%) were <60 years old and 326 (38%) were >80 years old.

At baseline, 621 (72%) patients were judged of normal weight, 164 (19%) were overweight and 74 (9%) underweight. The method of nutritional assessment was collected after the first 154 patients had been enrolled and hence was available in 703 (81.8%) patients (*Table 17*). In 489 (69.6%) patients, nutritional status was assessed informally (i.e. based on simple observation). Only 110 (15.7%) were weighed or had their BMI calculated, 75 (10.7%) were assessed by a dietitian, 62 (8.8%) had blood indices measured and 7 (1.0%) had anthropometry.

Following the stroke, the majority of patients were unable to talk and not orientated in terms of time, place and person (630/859, 73%) and only 27/859 (3.0%) were able to walk.

Only four (0.5%) misdiagnoses were made (two cerebral tumours, one TIA and one atrial fibrillation). These patients were included in the primary analyses.

The median delay from stroke onset to hospital admission was 0 days (IQR 0) in both treatment groups and patients were randomised a median of 3 days (IQR 3–4) after stroke onset. One patient

TABLE 16 *Baseline data in Trial 2*

		Avoid tube	Early tube	Total
Randomised		430	429	859
Sex	Female	231 (54%)	234 (55%)	465 (54%)
	Male	199 (46%)	195 (45%)	394 (46%)
Age (years)	⩽50	10 (2%)	22 (5%)	32 (4%)
	51–60	33 (8%)	23 (5%)	56 (7%)
	61–70	62 (14%)	67 (16%)	129 (15%)
	71–80	157 (37%)	159 (37%)	316 (37%)
	>80	168 (39%)	158 (37%)	326 (38%)
	Mean	76	76	76
	SD	11	11	11
	Median	78	78	78
	IQR	71–84	70–84	70–84
	Minimum, maximum	25, 98	34, 96	25, 98
Country	Australia	3 (0.7%)	2 (0.5%)	5 (0.6%)
	Belgium	8 (2%)	7 (2%)	15 (2%)
	Brazil	0 (0%)	1 (0.2%)	1 (0.1%)
	Canada	1 (0.2%)	1 (0.2%)	2 (0.2%)
	Czech Republic	7 (2%)	7 (2%)	14 (2%)
	Denmark	1 (0.2%)	0 (0%)	1 (0.1%)
	Hong Kong	7 (2%)	6 (1%)	13 (2%)
	India	12 (3%)	13 (3%)	25 (3%)
	Italy	65 (15%)	64 (15%)	129 (15%)
	New Zealand	34 (8%)	37 (9%)	71 (8%)
	Portugal	10 (2%)	10 (2%)	20 (2%)
	Republic of Ireland	2 (0.5%)	0 (0%)	2 (0.2%)
	Singapore	33 (8%)	34 (8%)	67 (8%)
	Turkey	14 (3%)	12 (3%)	26 (3%)
	UK	233 (54%)	235 (55%)	468 (54%)
Nutritional status	Underweight	40 (9%)	34 (8%)	74 (9%)
	Normal	308 (72%)	313 (73%)	621 (72%)
	Obese	82 (19%)	82 (19%)	164 (19%)
Lived alone before admission	Yes	120 (28%)	112 (26%)	232 (27%)
	Unknown	3 (0.7%)	1 (0.2%)	4 (0.5%)
Independent in everyday activities before stroke	Yes	358 (83%)	354 (83%)	712 (83%)
	Unknown	2 (0.5%)	3 (0.7%)	5 (0.6%)
Able to talk and orientated in time, place and person	Yes	117 (27%)	112 (26%)	229 (27%)
Could lift both arms	Yes	63 (15%)	75 (17%)	138 (16%)
Could walk unaided	Yes	11 (3%)	16 (4%)	27 (3%)
Predicted probability of poor outcome (%)	<40	20 (5%)	13 (3%)	33 (4%)
	40–80	29 (7%)	36 (8%)	65 (8%)
	80–90	39 (9%)	46 (11%)	85 (10%)
	90–95	36 (8%)	44 (10%)	80 (9%)
	>95	306 (71%)	290 (68%)	596 (69%)

was randomised a day late, on the eighth day of admission, but was included in the analyses.

Compliance with feeding regimes

Data on feeding regimes followed were available for 428 of 430 patients allocated to avoid tube feeding and all 429 allocated early tube feeding. Of the 429 patients allocated to early tube feeding, the randomising doctor stated a preference for the type of tube in 338 (78.8%) cases; 328 (76.5%) chose NG feeding and 10 (2.3%) PEG feeding. Fifty-two (12.1%) patients were co-enrolled into Trial 3 simultaneously, thus the type of tube was randomly allocated (26 to

TABLE 17 *Method of assessing nutritional status in Trial 2*[a]

		Avoid tube	Early tube	Total
Randomised		430	429	859
No discharge form		2	0	2
Nutritional status not recorded (old form)		75	79	154
Data available		353	350	703
Informal assessment	Yes	322 (91.2%)	313 (89.4%)	635 (90.3%)
	Unknown	0 (0%)	1 (0.3%)	1 (0.1%)
Informal assessment only	*Yes*	*249 (70.5%)*	*240 (68.6%)*	*489 (69.6%)*
	Unknown	0 (0%)	1 (0.3%)	1 (0.1%)
Weight/BMI	Yes	50 (14.2%)	60 (17.1%)	110 (15.7%)
	Unknown	0 (0%)	1 (0.3%)	1 (0.1%)
Dietitian's assessment	Yes	29 (8.2%)	46 (13.1%)	75 (10.7%)
	Unknown	0 (0%)	1 (0.3%)	1 (0.1%)
Anthropometry	Yes	3 (0.9%)	4 (1.1%)	7 (1.0%)
	Unknown	0 (0%)	1 (0.3%)	1 (0.1%)
Blood tests	Yes	35 (9.9%)	27 (7.7%)	62 (8.8%)
	Unknown	0 (0%)	1 (0.3%)	1 (0.1%)
Other	Nutrition scoring	6 (1.7%)	4 (1.1%)	10 (1.4%)
	Other	0 (0%)	1 (0.3%)	1 (0.1%)
	Not done	347 (98.3%)	344 (98.3%)	691 (98.3%)
	Unknown	0 (0%)	1 (0.3%)	1 (0.1%)

[a] Patients could be assessed using more than one method. The row in italics indicates where a test was used alone (and no other tests were done). All other rows show the numbers of patients who were assessed using a method either alone or in combination with other methods.

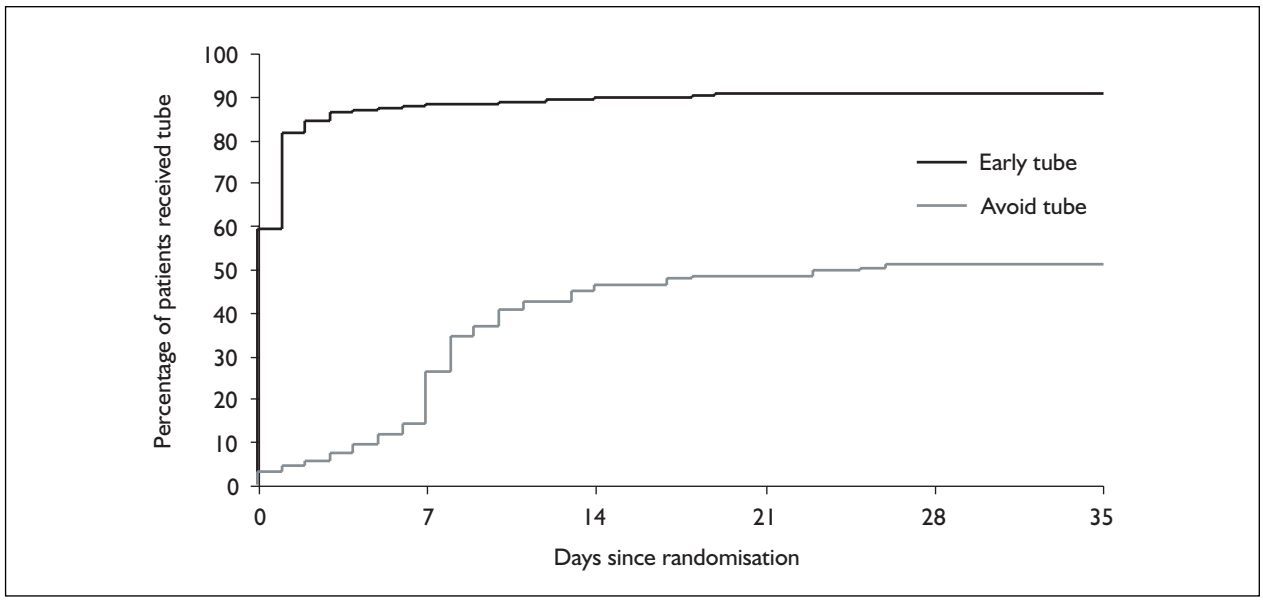

FIGURE 17 *Percentage of patients starting their allocated method of feeding during the first month after randomisation in Trial 2*

each type of tube). The timing of starting any tube feeding in each treatment group is shown in *Figure 17*. A significant proportion of patients were not compliant with the treatment in terms of timing; 60/429 (14%) did not receive early tube feeding within 3 days of randomisation. A total of 354 (82.5%) allocated early feeding received NG feeding, 36 a PEG first and 83 (19.3%) a PEG at some point. For those allocated to avoid tube feeding for at least 1 week 58 (13.6%) received

TABLE 18 *Type and duration of enteral tube feeding in Trial 2*[a]

		Avoid tube	Early tube	Total
	Randomised	430	429	859
Number of NG tubes used	Number with data	154	354	508
	Median	2	2	2
	IQR	1–4	1–3	1–3
	Minimum, maximum	1, 11	1, 18	1, 18
	Mean	2.7	2.5	2.6
	SD	2.0	2.1	2.0
Total duration of NG tube feeding (days)	Number with data	155	356	511
	Median	10	9	10
	IQR	4–21	5–18	5–19
	Minimum, maximum	0.5, 76	0.5, 120	0.5, 120
	Mean	15	14	14
	SD	14	16	15
Average time that each NG tube stayed in each patient (days)	Number with data	154	354	508
	Median	4	5	5
	IQR	2–10	3–10	2–10
	Minimum, maximum	0.3, 46	0.03, 56	0.03, 56
	Mean	7	7	7
	SD	8	7	7
Number of PEG tubes used	Number with data	69	83	152
	Median	1	1	1
	IQR	1–1	1–1	1–1
	Minimum, maximum	1, 2	1, 1	1, 2
	Mean	1.1	1.0	1.0
	SD	0.2	0.0	0.2
Total duration of PEG tube feeding (days)	Number with data	69	83	152
	Median	32	28	29
	IQR	13–65	12–55	13–57
	Minimum, maximum	3, 178	1, 219	1, 219
	Mean	47	42	44
	SD	46	43	44
Average time that each PEG tube stayed in each patient (days)	Number with data	69	83	152
	Median	30	28	28
	IQR	13–63	12–55	13–55
	Minimum, maximum	3, 178	1, 219	1, 219
	Mean	46	42	44
	SD	45	43	44

[a] If the tube was inserted and taken out on the same day, this has been counted as 0.5 days duration. Patients who did not get tubes at all are not counted here.

tube feeding within 7 days of randomisation. Eventually 154 (35.8%) received NG feeding and 32 (7.5%) received PEG feeding first. Eventually 69 of the 430 patients had PEG inserted. In total, 242 (56.5%) received neither NG nor PEG feeding.

The reasons for non-compliance included the death of the patient before tube feeding could be started, improvement in swallowing ability, change of mind by staff, patient or relative or simple errors in recording the allocated treatment. Tube feeding was often delayed because of the difficulty in accessing early PEG.

The duration of PEG feeding was considerably longer than NG feeding (median 29 days, IQR 13–57 compared with 10 days, IQR 5–19) and also the average time each tube stayed in place [median 28 days (IQR 13–55) compared with 5 days (IQR 2–10)]. The median number of PEGs was one (IQR 1–2) compared with two NGs (IQR 1–3, maximum 18). These data are presented in more detail in *Table 18*. The proportion of patients who had died, who were receiving either NG feeding, PEG feeding or neither in hospital and the proportion discharged are shown in *Figure 18*.

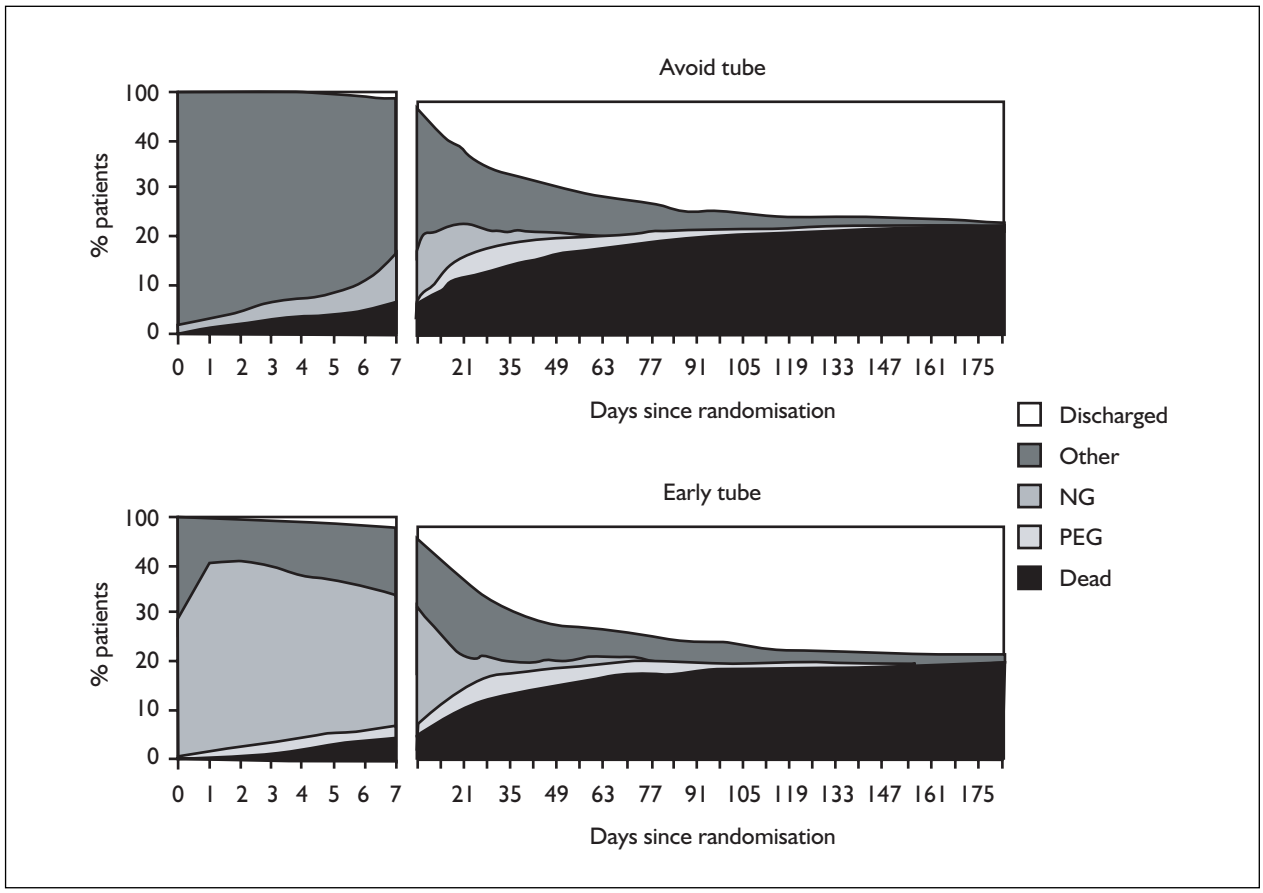

FIGURE 18 *Percentage of patients receiving either enteral tube feeding via PEG or NG feeding or other (none, parenteral fluids or oral) following randomisation to hospital discharge, the percentage discharged or dying in Trial 2. Note it includes death following discharge but does not show the proportion receiving tube feeding after discharge.*

Adverse events

Of the 389 deaths reported, 12 (3.1%) were attributed to the trial treatment by the responsible physician, five in the avoid tube feeding group (three died after NG insertion and two after PEG insertion) and seven in the early tube group (five after NG insertion and two after PEG).

Causes of death

A total of 289 deaths were reported, of which 207 were in the avoid tube feeding arm and 182 in the early feeding arm. The vital status of one patient was unknown in the avoid arm. The most common causes of death were pneumonia [74/207 (35.8%) in the avoid group and 77/182 (42.3%) in the early tube group] and the initial stroke (104/389, 26.7%). There were more non-vascular deaths in the avoid group than the early tube group [21/207 (10.1%) versus 7/182 (3.9%)]. These are described in *Table 19*.

Primary outcome

The sample size calculations were based on a dichotomous outcome – death or poor outcome (MRS 4–5) at follow-up. The two primary analyses are based on death or poor outcome and overall survival, subdivided by allocated treatment, irrespective of compliance.

The numbers and proportion of enrolled patients who died and the MRS of survivors in each treatment arm are given in *Table 20* (and graphically in *Figures 19* and *20*).

Allocation to early tube feeding was associated with a non-significant reduction in absolute risk of death of 5.8% (95% CI –0.8 to 12.5%, $p = 0.09$). The absolute reduction in the risk of death or poor outcome was in the same direction but much more modest (1.2%, 95% CI –4.2 to 6.6%, $p = 0.7$). The unadjusted risk differences are shown graphically in *Figure 21* and the effect of adjusting for any baseline imbalance in minimisation variables is shown in *Table 21*. There was no significant difference between the Kaplan–Meier survival curves (log-rank test, $p = 0.14$, *Figure 22*); however, there is a trend towards patients allocated to early feeding surviving slightly longer.

TABLE 19 *Causes of death in Trial 2*

	Avoid tube	Early tube	Total
Initial stroke	55 (26.6%)	49 (26.9%)	104 (26.7%)
Pneumonia	74 (35.8%)	77 (42.3%)	151 (38.8%)
Pulmonary embolism	7 (3.4%)	6 (3.3%)	13 (3.3%)
Recurrent stroke	26 (12.6%)	20 (11.0%)	46 (11.8%)
Coronary heart disease	7 (3.4%)	6 (3.3%)	13 (3.4%)
Other vascular	17 (8.2%)	15 (8.2%)	32 (8.2%)
Sudden death	2	1	3
Stroke/cerebrovascular disease	6	2	8
Acute coronary syndrome	3	1	4
GI haemorrhage	1	3	4
Cardiac failure	1	5	6
Peripheral	4	2	6
Uncertain cause	0	1	1
Other non-vascular	21 (10.1%)	7 (3.9%)	28 (7.2%)
Carcinoma	5	2	7
Old age (on death certificate)	1	0	1
Respiratory failure	4	1	5
Sepsis	6	4	10
Dementia	0	0	0
Renal failure	2	0	2
Other	3	0	3
Missing	0 (0%)	2 (1.1%)	2 (0.5%)
Total	207	182	389

TABLE 20 *Number and proportion of patients with each MRS score, with our primary outcome and death by treatment allocation in Trial 2*

	Avoid tube		Early tube		Risk difference (%)	
MRS Score	*n*	**%**	*n*	**%**	**Difference**	**95% CI**
0	9	2.1	4	0.9		
1	16	3.7	10	2.3		
2	19	4.4	26	6.1		
3	41	9.5	50	11.7		
4	42	9.8	53	12.4		
5	95	22.1	104	24.2		
Dead	207	48.1	182	42.4	–5.8	–12.5 to 0.8
Unknown	1	0.2	0	0		
MRS 0–3	85	19.8	90	21.0		
MRS 4–5	137	31.9	157	36.6		
Dead or MRS 4–5	344	80.0	339	79.0	–1.2	–6.6 to 4.2
Total	430		429			

TABLE 21 *Effect of adjusting for any baseline imbalance in minimisation variables in Trial 2*[a]

Outcome		OR	95% CI	*p*-Value
Dead or MRS 4–5	Unadjusted	0.931	0.67 to 1.30	0.672
	Adjusted[b]	0.932	0.64 to 1.35	0.707
Dead	Unadjusted	0.790	0.60 to 1.03	0.086
	Adjusted[b]	0.803	0.60 to 1.07	0.135

[a] This was not a prespecified analysis but is often recommended by trial statisticians.
[b] Adjusted analyses have been adjusted for variables from the minimisation algorithm: country (Italy, Singapore, New Zealand, UK, other), age (<75, >75 years), sex, probability of poor outcome (<0.8, >0.8) and nutritional status (normal, undernourished, overweight).

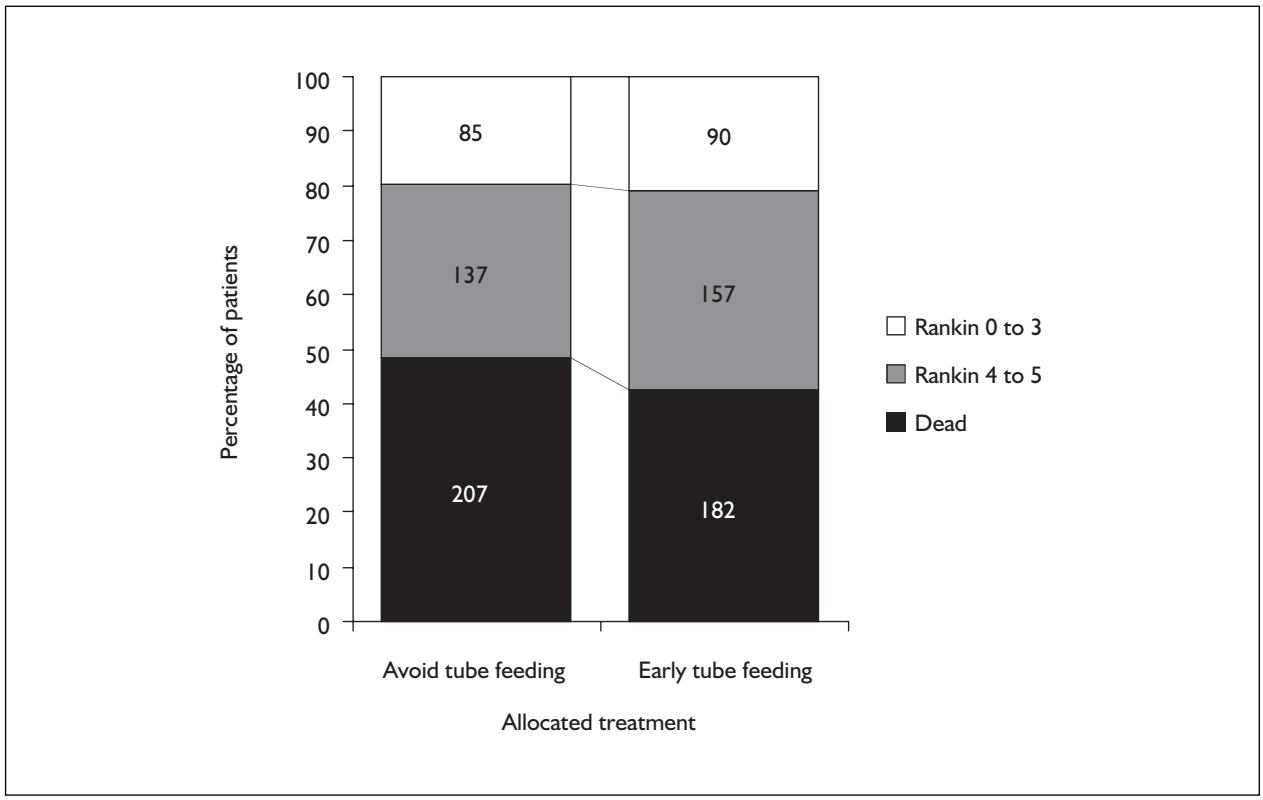

FIGURE 19 *Proportion of patients in each treatment group with primary outcomes in Trial 2. Patients with missing outcomes have been omitted as there are too few of them to show up.*

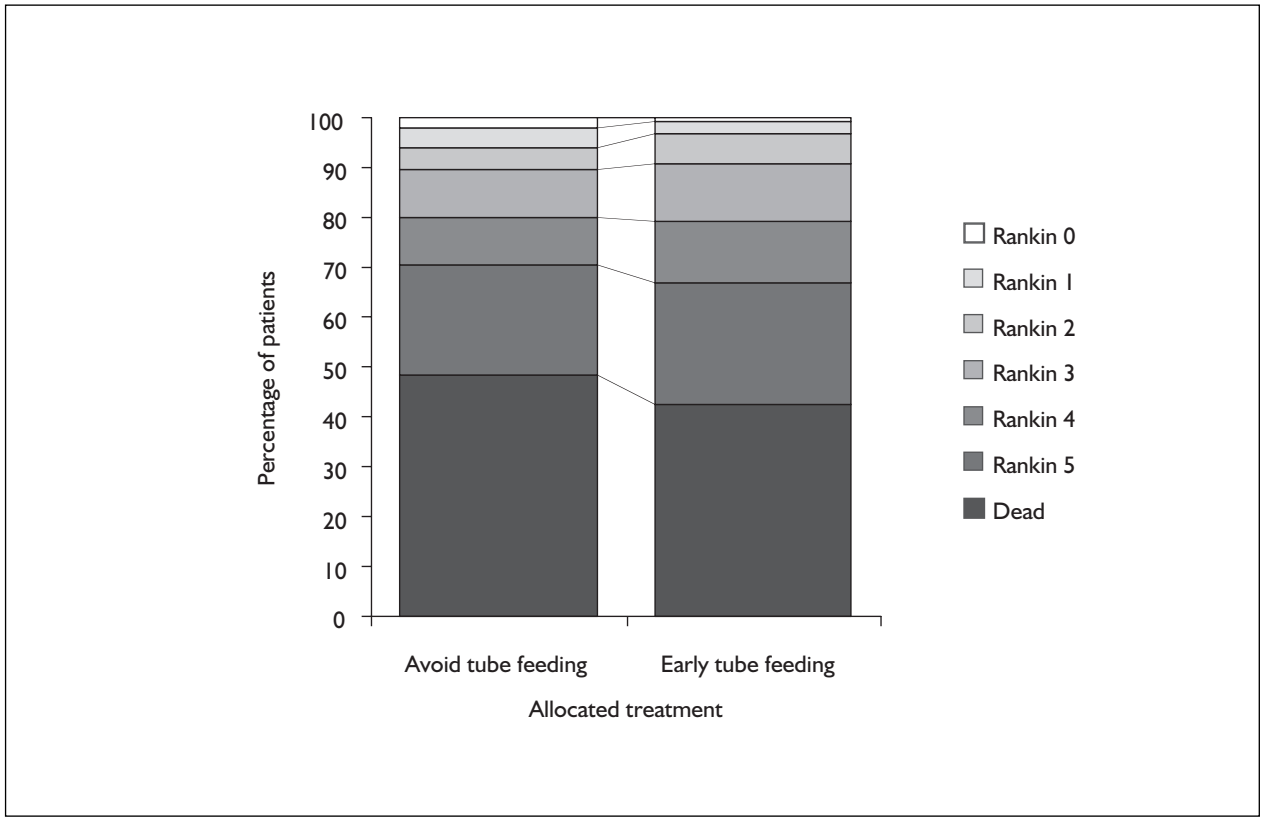

FIGURE 20 *Percentage of patients with each MRS at follow-up in each treatment group in Trial 2*

Outcome	Early tube *n*/*N* (%)	Avoid tube *n*/*N* (%)	Risk difference (95% CI)	*p*-Value
Modified Rankin 4–6 versus 0–2	339/429 (79.0%)	344/429 (80.2%)	–0.012 (–0.066 to +0.042)	0.672
Death	182/429 (42.4%)	207/429 (48.3%)	–0.058 (–0.125 to +0.008)	0.086

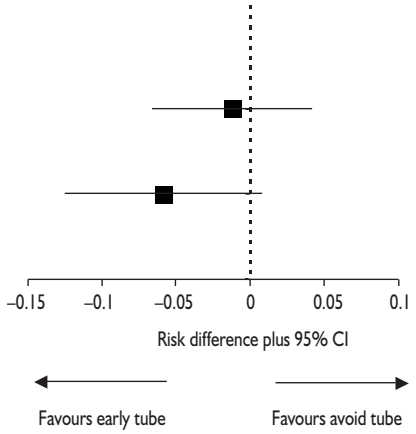

FIGURE 21 *Risk ratios comparing the primary outcomes of the two treatment groups in Trial 2*

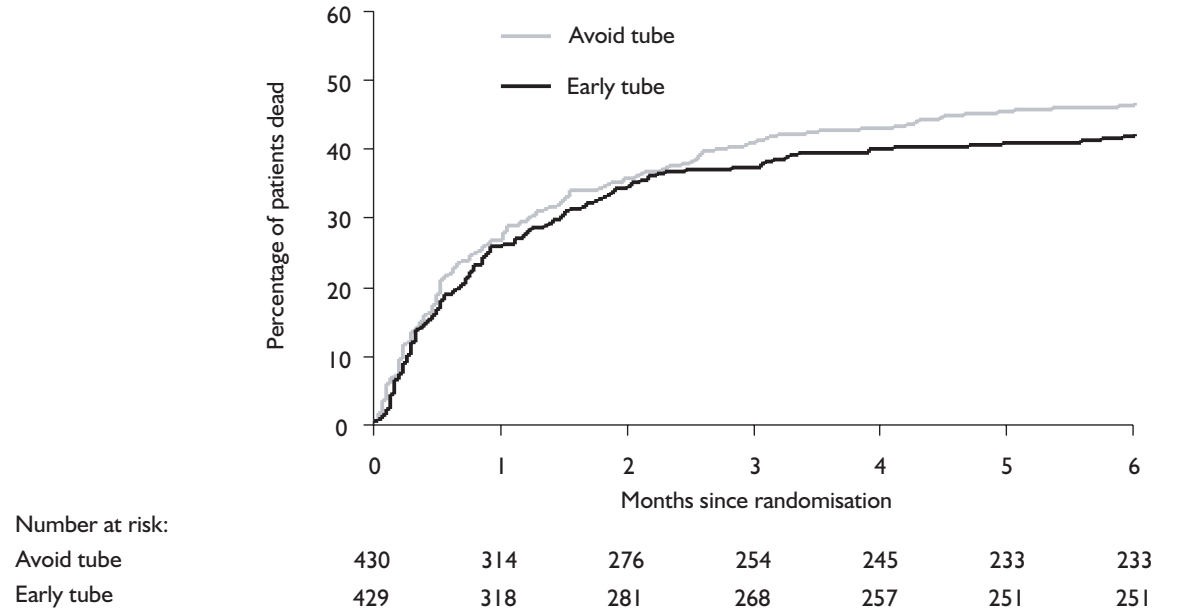

FIGURE 22 *Kaplan–Meier survival curves for the two treatment groups in Trial 2*

Secondary outcomes

In-hospital complications

The rates of in-hospital complications in the two treatment groups are shown in *Table 22*. Pneumonia and urinary infections were the commonest reported complications [265/857 (30.9%) and 131/857 (15.3%), respectively]. There was a higher rate of gastrointestinal haemorrhages in the early tube group [22/429 (5.1%)] compared with the avoid tube group [11/428 (2.6%), $p = 0.04$]. Of the 22 allocated early feeding gastrointestinal haemorrhages occurred in 14 patients while an NG was *in situ*, six after an NG tube had been removed and two while a PEG was *in situ*. Seven bleeds were major (requiring intervention, transfusion or leading to death), four fatal and in the remainder it was not stated. In those 11 allocated to avoid tube feeding for at least 1 week, gastrointestinal haemorrhages occurred in five patients with an NG *in situ*, two with a PEG, two post-PEG and two without any enteral tube feeding. Two were major (one fatal), two were minor and in the remainder it was unclear. Six were upper gastrointestinal

TABLE 22 *Secondary outcomes – in-hospital complications in Trial 2*

Outcome	Avoid tube	Early tube	Total	Log-rank *p*-value
Randomised	430	429	859	
No discharge form	2	0	2	
Data available	428	429	857	
Recurrent stroke	23 (5.4%)	15 (3.5%)	38 (4.4%)	0.20
Neurological worsening	59 (13.8%)	44 (10.3%)	103 (12.0%)	0.13
Pneumonia	133 (31.1%)	132 (30.8%)	265 (30.9%)	>0.9
Pneumonia but date?	1 (0.2%)	2 (0.5%)	3 (0.4%)	
Pulmonary embolism	8 (1.9%)	6 (1.4%)	14 (1.6%)	0.60
Deep-vein thrombosis	13 (3.0%)	11 (2.6%)	24 (2.8%)	0.71
Pressure sores	10 (2.3%)	12 (2.8%)	22 (2.6%)	0.84
GI haemorrhage	11 (2.6%)	22 (5.1%)	33 (3.9%)	0.043
UTI/cystitis including MRSA	65 (15.2%)	66 (15.4%)	131 (15.3%)	>0.9
UTI but date?	4 (0.9%)	1 (0.2%)	5 (0.6%)	
PEG site including MRSA	12 (2.8%)	6 (1.4%)	18 (2.1%)	0.06[b]
Skin conditions	10 (2.3%)	8 (1.9%)	18 (2.1%)	0.63
Other infections[a]	35 (8.2%)	29 (6.8%)	64 (7.5%)	0.38
Other but date?	1 (0.2%)	0 (0%)	1 (0.1%)	
Diarrhoea	6 (1.4%)	8 (1.9%)	14 (1.6%)	0.83[b]
Diarrhoea but date?	4 (0.9%)	4 (0.9%)	8 (0.9%)	
Neurological condition	7 (1.6%)	11 (2.6%)	18 (2.1%)	0.47
Acute coronary/cardiac arrest	13 (3.0%)	7 (1.6%)	20 (2.3%)	0.18
Electrolyte disturbance	10 (2.3%)	3 (0.7%)	13 (1.5%)	0.052
Renal/urinary problem	6 (1.4%)	7 (1.6%)	13 (1.5%)	>0.9[b]
Renal but date?	2 (0.5%)	1 (0.2%)	3 (0.4%)	
Gastric/bowel	7 (1.6%)	5 (1.2%)	12 (1.4%)	0.61
Psychiatric	9 (2.1%)	3 (0.7%)	12 (1.4%)	0.09
Peripheral vascular disease	5 (1.2%)	7 (1.6%)	12 (1.4%)	0.55
Cardiac failure	7 (1.6%)	12 (2.8%)	19 (2.2%)	0.26
Other medical complications[c]	30 (7.0%)	25 (5.8%)	55 (6.4%)	
Yes but date?	1 (0.2%)	4 (0.9%)	5 (0.6%)	0.55

[a] 'Other' includes all categories of infections that were experienced by ≤ 10 patients (including infections of eye, mouth, bile, Venflon/subcut site, MRSA infections, *C. difficile* infections, infections of known origin, infections of unknown origin, other infections).
[b] This is from a Fisher's exact test. There were too many missing dates to use a log-rank test.
[c] 'Other' includes all categories of medical complications experienced by ≤ 10 patients (including MRSA colonisation, haemorrhage, hyper-/hypoglycaemia, skeleton/joint/trauma, carcinoma).

haemorrhages [from duodenal ulcers (two), gastritis (one), upper gastrointestinal cancer (two)]. In the remainder the source was unclear.

Length of hospital stay and discharge destination

LOS was available for 857 (99.8%) and the median LOS was 24 days in both groups [avoid tube feeding, IQR 12–58, mean 44, SD 50; early tube feeding, IQR 12–53, mean 45, SD 58; difference of means –1.3 days (95% CI –8.6 to +5.9)]. One-quarter of all patients were discharged home with a partner or relative [211 (24.6 %)] and 138 (16.1%) were discharged to a nursing home. There were no significant differences in the discharge destinations between the two groups (*Table 23*). There was also no significant difference in patients' residence at final follow-up (*Table 24*). One hundred patients died between discharge and follow-up.

TABLE 23 *Discharge destination in Trial 2*

	Avoid tube	Early tube	Total
Randomised	430	429	859
Own home alone	21 (4.9%)	14 (3.3%)	35 (4.1%)
At home, with partner/relative	104 (24.2%)	107 (24.9%)	211 (24.6%)
Relative's home	8 (1.9%)	12 (2.8%)	20 (2.3%)
Residential home	11 (2.6%)	7 (1.6%)	18 (2.1%)
Nursing home	69 (16.1%)	69 (16.1%)	138 (16.1%)
Other hospital	45 (10.5%)	42 (9.8%)	87 (10.1%)
Other	22 (5.1%)	35 (8.2%)	57 (6.6%)
Specialist ward	0	3	3
Hospital	2	1	3
Rehab/nursing home	20	30	50
Own home/sheltered housing	0	1	1
Not discharged from hospital	1 (0.2%)	1 (0.2%)	2 (0.2%)
Dead	147 (34.2%)	142 (33.1%)	289 (33.6%)
No discharge form	2 (0.5%)	0 (0%)	2 (0.2%)

TABLE 24 *Residence at follow-up in Trial 2*

Residence	Avoid tube	Early tube	Total
Randomised	430	429	859
Own home alone	14 (3.3%)	17 (4.0%)	31 (3.6%)
Own/relative's home with partner/relative	122 (28.4%)	136 (31.7%)	258 (30.0%)
Residential home	13 (3.0%)	15 (3.5%)	28 (3.3%)
Nursing home	58 (13.5%)	58 (13.5%)	116 (13.5%)
Alive, not in hospital, but otherwise unknown	0 (0%)	0 (0%)	0 (0%)
Hospital	15 (3.5%)	21 (4.9%)	36 (4.2%)
Dead	207 (48.1%)	182 (42.4%)	389 (45.3%)
No follow-up	1 (0.2%)	0 (0%)	1 (0.1%)

TABLE 25 *Method of feeding at final follow-up in Trial 2*

Method	Avoid tube	Early tube	Total
Randomised	430	429	859
Normal feeding	189 (44.0%)	203 (47.3%)	392 (45.6%)
NG tube	10 (2.3%)	14 (3.3%)	24 (2.8%)
PEG tube	23 (5.4%)	30 (7.0%)	53 (6.2%)
Alive, but method unknown	0 (0%)	0 (0%)	0 (0%)
Dead	207 (48.1%)	182 (42.4%)	389 (45.3%)
No follow-up	1 (0.2%)	0 (0%)	1 (0.1%)

Method of feeding at final follow-up

Table 25 shows the method of feeding in patients surviving to final follow-up. There were no important differences between the two treatment groups.

Quality of life (EuroQoL)

Complete QoL data were available for 421 (98.1%) patients in the early tube arm and 428 (99.5%) in the avoid tube arm. There were no significant differences between treatment groups (*Table 26*). The median utility (including dead patients who have a utility of zero) was 0.00 in both groups ($p = 0.76$) [difference of means (avoid tube – early tube) +0.013 (95% CI –0.028 to +0.053)], but if dead patients were excluded the utility was marginally better for patients allocated to the avoid tube arm rather than the early feeding arm (0.15 versus 0.08; $p = 0.35$) (see *Figure 23*).

TABLE 26 *Quality of life (EuroQOL) at final follow-up in Trial 2*

	Avoid	Early	Total
Randomised	430	429	859
Mobility			
No problems	38 (8.8%)	22 (5.1%)	60 (7.0%)
Some problems	95 (22.1%)	123 (28.7%)	218 (25.4%)
Confined to bed	89 (20.7%)	102 (23.8%)	191 (22.2%)
Alive, data unknown	0 (0%)	0 (0%)	0 (0%)
Dead	207 (48.1%)	182 (42.4%)	389 (45.3%)
No follow-up	1 (0.2%)	0 (0%)	1 (0.1%)
Self-care			
No problems	39 (9.1%)	28 (6.5%)	67 (7.8%)
Some problems	67 (15.6%)	88 (20.5%)	155 (18.0%)
Unable	116 (27.0%)	131 (30.5%)	247 (28.8%)
Alive, data unknown	0 (0%)	0 (0%)	0 (0%)
Dead	207 (48.1%)	182 (42.4%)	389 (45.3%)
No follow-up	1 (0.2%)	0 (0%)	1 (0.1%)
Usual activities			
No problems	23 (5.4%)	14 (3.3%)	37 (4.3%)
Some problems	59 (13.7%)	66 (15.4%)	125 (14.6%)
Unable	140 (32.6%)	167 (38.9%)	307 (35.7%)
Alive, data unknown	0 (0%)	0 (0%)	0 (0%)
Dead	207 (48.1%)	182 (42.4%)	389 (45.3%)
No follow-up	1 (0.2%)	0 (0%)	1 (0.1%)
Pain/discomfort			
None	88 (20.5%)	89 (20.8%)	177 (20.6%)
Moderate	116 (27.0%)	133 (31.0%)	249 (29.0%)
Extreme	17 (4.0%)	20 (4.7%)	37 (4.3%)
Alive, data unknown	1 (0.2%)	5 (1.2%)	6 (0.7%)
Dead	207 (48.1%)	182 (42.4%)	389 (45.3%)
No follow-up	1 (0.2%)	0 (0%)	1 (0.1%)
Anxiety/depression			
None	83 (19.3%)	74 (17.3%)	157 (18.3%)
Moderate	117 (27.2%)	134 (31.2%)	251 (29.2%)
Extreme	21 (4.9%)	34 (7.9%)	55 (6.4%)
Alive, data unknown	1 (0.2%)	5 (1.2%)	6 (0.7%)
Dead	207 (48.1%)	182 (42.4%)	389 (45.3%)
No follow-up	1 (0.2%)	0 (0%)	1 (0.1%)

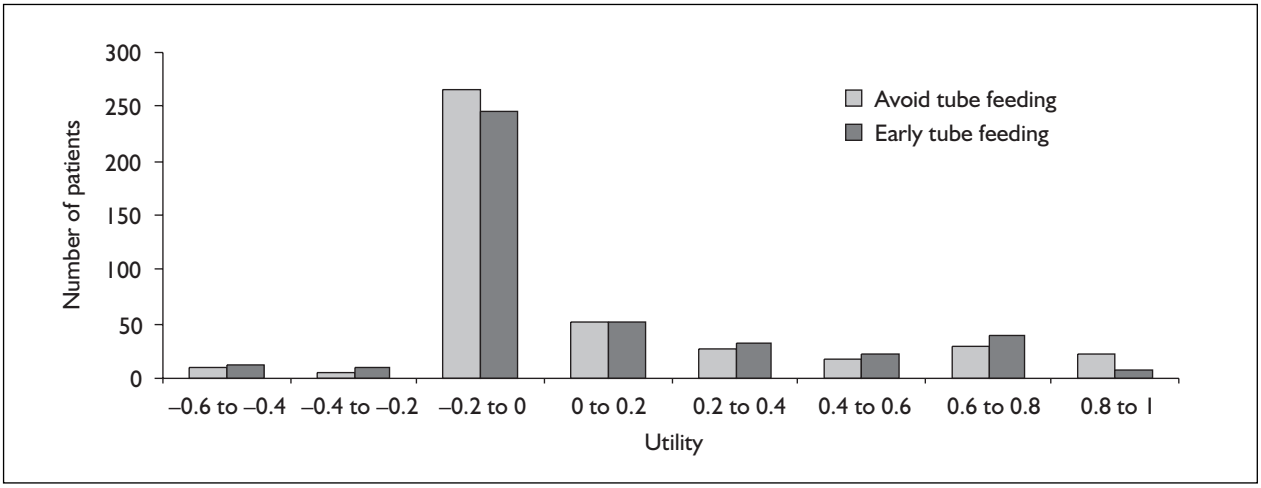

FIGURE 23 *Distribution of utilities (based on EuroQol) for the two treatment groups in Trial 2*

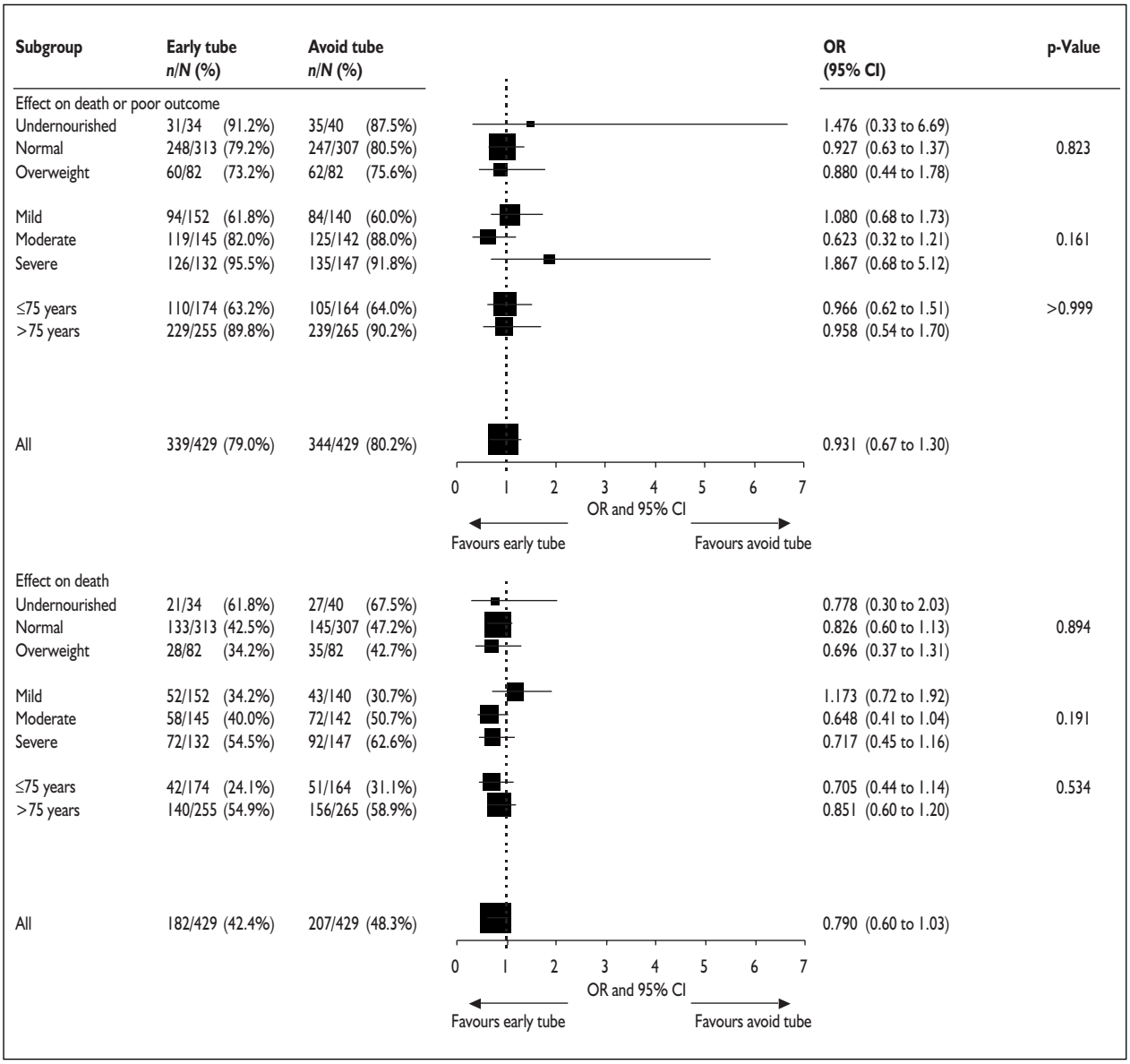

FIGURE 24 *Effect of early tube feeding versus avoid tube feeding on both primary outcomes subdivided by baseline characteristics in Trial 2. Results are expressed as OR and 95% CI.*

Subgroup analyses

The primary outcomes of patients subdivided by age, baseline nutritional status and tertiles of predicted stroke outcome are shown in *Figure 24*. There was no significant heterogeneity of treatment effect between subgroups.

Trial 3: NG tube feeding versus PEG tube feeding

A total of 321 patients were recruited into Trial 3, of whom 83 were randomised during the start-up phase (from 19 November 1996 to 25 October 1998). The remaining 238 patients were randomised during the main phase of the trial from 26 October 1998 to 14 July 2003.

Of the 321 patients enrolled into the trials, 98 (30.5%) were co-enrolled into more than one trial. Eighteen patients were enrolled into Trials 1 and 3 only. Eight were enrolled into Trial 1 followed by Trial 3. The median time between enrolling in Trial 1 and enrolling in Trial 3 was 14 days (IQR 7–14, minimum 4, maximum 15 days). Ten were enrolled into Trial 3 followed by Trial 1. The median time between enrolling in Trial 3 and enrolling in Trial 1 was 13 days (IQR 7–20, minimum 3, maximum 27 days). Seventy-seven patients were enrolled into Trials 2 and 3 only.

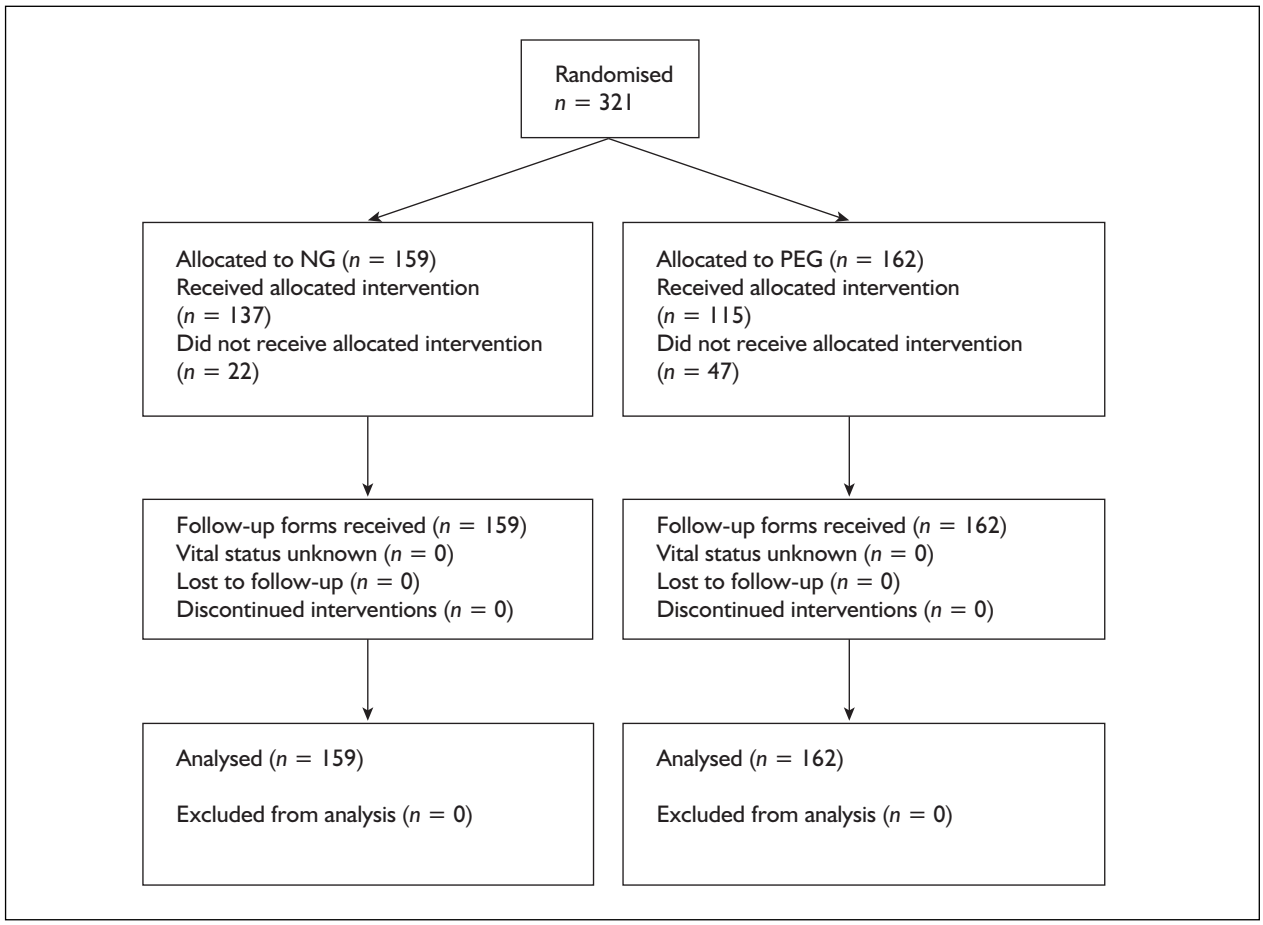

FIGURE 25 *CONSORT diagram for Trial 3*

Twenty-seven were enrolled into Trial 2 followed by Trial 3. The median time between enrolling in Trial 2 and enrolling in Trial 3 was 9 days (IQR 7–11, minimum 5, maximum 22 days). Ten were allocated avoid and then NG, 12 avoid and then PEG, two early NG and three early PEG. Fifty were enrolled into Trials 2 and 3 concurrently. Twenty-five were allocated early NG and 25 early PEG. Three patients were enrolled into Trials 1, 2 and 3. One was enrolled into Trial 2, then Trial 1 (5) days later), then Trial 3 (7 days later). This patient was allocated avoid in Trial 2 and PEG in Trial 3. Two were enrolled into Trials 2 and 3 concurrently, followed by Trial 1 (7 and 20 days later). These patients were both allocated early tube in Trial 2, but one was allocated NG, and one PEG in Trial 3.

Data completeness

In total, 321 patients were randomised into Trial 3 (159 to NG and 162 to PEG). All 100% of baseline data were collected at randomisation; thereafter, all discharge and follow-up forms were received. No patients were lost to follow-up (see CONSORT diagram, *Figure 25*). Data on compliance, in-hospital complications and follow-up were collected until 5 April 2004, when the database was closed.

The follow-up data were collected in surviving patients at a median of 6.2 months (IQR 5.7–7.5) after randomisation in the NG group compared with 6.6 months (IQR 5.8–7.7) in the PEG group (Wilcoxon test, $p = 0.32$). Of the 321 follow-ups completed, 155 (48.3%) patients had died and the forms were completed by a spouse, relative, friend or carer in 139 (43.3%), by the patient in only 19 (5.9%), by a doctor in seven (2.2% and by an unknown person in one (0.3%).

Baseline data

Table 27 shows the baseline data. Forty-seven centres in 11 countries randomised patients into Trial 3. A total of 260 (81%) were from the UK. Minimisation at randomisation ensured balance between treatment group, with respect to sex, age, nutritional status and predicted outcome. In total, 144 (45%) were male with a mean age in both groups of 76 years (range: 42–98 years); 27 (8%) were <60 years old and 113 (35%) were >80 years old.

TABLE 27 *Baseline data in Trial 3*

		NG tube	PEG tube	Total
Randomised		159	162	321
Sex	Female	88 (55%)	89 (55%)	177 (55%)
	Male	71 (45%)	73 (45%)	144 (45%)
Age (years)	≤ 50	6 (4%)	5 (3%)	11 (3%)
	51–60	6 (4%)	10 (6%)	16 (5%)
	61–70	22 (14%)	27 (17%)	49 (15%)
	71–80	64 (40%)	68 (42%)	132 (41%)
	>80	61 (38%)	52 (32%)	113 (35%)
	Mean	77	76	76
	SD	10	10	10
	Median	78	78	77
	IQR	72–84	71–84	71–84
	Minimum, maximum	42, 98	45, 96	42, 98
Country	Australia	1 (0.6%)	2 (1%)	3 (0.9%)
	Belgium	3 (2%)	2 (1%)	5 (2%)
	Brazil	2 (1%)	2 (1%)	4 (1%)
	Czech Republic	5 (3%)	7 (4%)	12 (4%)
	Denmark	1 (0.6%)	1 (0.6%)	2 (0.6%)
	Hong Kong	1 (0.6%)	0 (0%)	1 (0.3%)
	Italy	3 (2%)	2 (1%)	5 (2%)
	New Zealand	3 (2%)	6 (4%)	9 (3%)
	Republic of Ireland	2 (1%)	1 (0.6%)	3 (0.9%)
	Singapore	8 (5%)	9 (6%)	17 (5%)
	UK	130 (82%)	130 (80%)	260 (81%)
Nutritional status	Underweight	34 (21%)	36 (22%)	70 (22%)
	Normal	100 (63%)	96 (59%)	196 (61%)
	Obese	25 (16%)	30 (19%)	55 (17%)
Lived alone before admission	Yes	50 (31%)	57 (35%)	107 (33%)
	No	108 (68%)	104 (64%)	212 (66%)
	Unknown	1 (0.6%)	1 (0.6%)	2 (0.6%)
Independent in every day activities before stroke	Yes	126 (79%)	135 (83%)	261 (81%)
	No	31 (20%)	27 (17%)	58 (18%)
	Unknown	2 (1%)	0 (0%)	2 (0.6%)
Able to talk and orientated in time, place and person	Yes	40 (25%)	40 (25%)	80 (25%)
	No	119 (75%)	122 (75%)	241 (75%)
Could lift both arms	Yes	27 (17%)	24 (15%)	51 (16%)
	No	132 (83%)	138 (85%)	270 (84%)
Could walk unaided	Yes	6 (4%)	4 (2%)	10 (3%)
	No	153 (96%)	158 (98%)	311 (97%)
Predicted probability of poor outcome (%)	<40	4 (3%)	6 (4%)	10 (3%)
	40–80	11 (7%)	10 (6%)	21 (7%)
	80–90	11 (7%)	10 (6%)	21 (7%)
	90–95	13 (8%)	18 (11%)	31 (10%)
	>95	120 (75%)	118 (73%)	238 (74%)

At baseline 196 (61%) patients were judged normal weight, 55 (17%) overweight and 70 (22%) underweight. The proportion judged underweight was much higher in this trial than in Trials 1 and 2. Twenty-seven of 131 (20.6%) patients were diabetic (data for the remaining 190 patients are unknown because these data were only collected during the main phase of the trial). The method of nutritional assessment was collected after the first 76 patients had been enrolled and hence was available in 245 (76.3%) patients (*Table 28*). In 198/245 (80.8%), the patients' nutritional status was assessed informally (i.e. based purely on simple observation). In total, 72/245 (29.4%) were weighed or had their BMI calculated, 92/245 (37.6%) were assessed by a

TABLE 28 *Method of assessing nutritional status in Trial 3*[a]

		NG tube	PEG tube	Total
Randomised		159	162	321
No discharge form		0	0	0
Nutritional status not recorded (old form)		38	38	76
Data available		121	124	245
Informal assessment	Yes	100 (82.6%)	98 (79.0%)	198 (80.8%)
	No	21 (17.4%)	25 (20.2%)	46 (18.8%)
	Unknown	0 (0%)	1 (0.8%)	1 (0.4%)
Informal assessment only	*Yes*	*38 (31.4%)*	*51 (41.1%)*	*89 (36.3%)*
	No	*83 (68.6%)*	*72 (58.1%)*	*155 (63.3%)*
	Unknown	*0 (0%)*	*1 (0.8%)*	*1 (0.4%)*
Weight/BMI	Yes	38 (31.4%)	34 (27.4%)	72 (29.4%)
	No	83 (68.6%)	89 (71.8%)	172 (70.2%)
	Unknown	0 (0%)	1 (0.8%)	1 (0.4%)
Dietitian's assessment	Yes	44 (36.4%)	48 (38.7%)	92 (37.6%)
	No	77 (63.6%)	75 (60.5%)	152 (62%)
	Unknown	0 (0%)	1 (0.8%)	1 (0.4%)
Anthropometry	Yes	3 (2.5%)	1 (0.8%)	4 (1.6%)
	No	118 (97.5%)	122 (98.4%)	240 (98.0%)
	Unknown	0 (0%)	1 (0.8%)	1 (0.4%)
Blood tests	Yes	45 (37.2%)	33 (26.6%)	78 (31.8%)
	No	76 (62.8%)	90 (72.6%)	166 (67.8%)
	Unknown	0 (0%)	1 (0.8%)	1 (0.4%)
Other	Nutrition scoring	2 (1.7%)	4 (3.2%)	6 (2.5%)
	Other	0 (0%)	1 (0.8%)	1 (0.4%)
	Not done	119 (98.4%)	118 (95.2%)	237 (96.7%)
	Unknown	0 (0%)	1 (0.8%)	1 (0.4%)

[a] Patients could be assessed using more than one method. The rows in italics indicate where a test was used alone (and no other tests were done). All other rows show the numbers of patients who were assessed using a method either alone or in combination with other methods.

dietitian, 78/245 (31.8%) had blood indices measured and 4/245 (1.6%) had anthropometric measurements taken. The greater proportion of patients having more detailed assessment of baseline nutritional status in Trial 3 than the other trials may have been due to the longer interval between hospital admission and randomisation.

No misdiagnoses were made. The median delay from stroke onset to admission was 0 days (IQR 0) and between admission and randomisation 8 days (IQR 4–12).

Feeding and compliance to treatment allocation

Almost all PEG tubes, 187/189 (99%), were actually gastric tubes, with only two having either a duodenal or jejunal tube. Most [182/189 (96.3%)] were placed endoscopically but seven were placed under radiological guidance (3.7%).

Of the 159 patients allocated to receive an NG tube, 137 (86.2%) received NG (including 44 who were later changed to a PEG tube). Of the remaining 22, nine received neither NG nor PEG tube feeding and 13 received PEG tube feeding only. Only this last group is strictly a 'cross-over' to the other treatment arm. Of the 162 patients allocated PEG, 78 (48.1%) received a PEG tube within 3 days and 115 (71.0%) received a PEG tube prior to any NG. Of the others, 21 received neither NG nor PEG tube feeding, 17 received an NG tube then a PEG tube and nine received only NG tube feeding. Only these last two groups are strictly 'cross-overs' to the other treatment arm. Of the 321 randomised into Trial 3, 69 (21.4%) were non-compliant [22/159 (13.8%) in the NG group and 47/162 (29.0%) in the PEG group]. *Figure 26* shows the intervals between randomisation and first placement of the allocated tube.

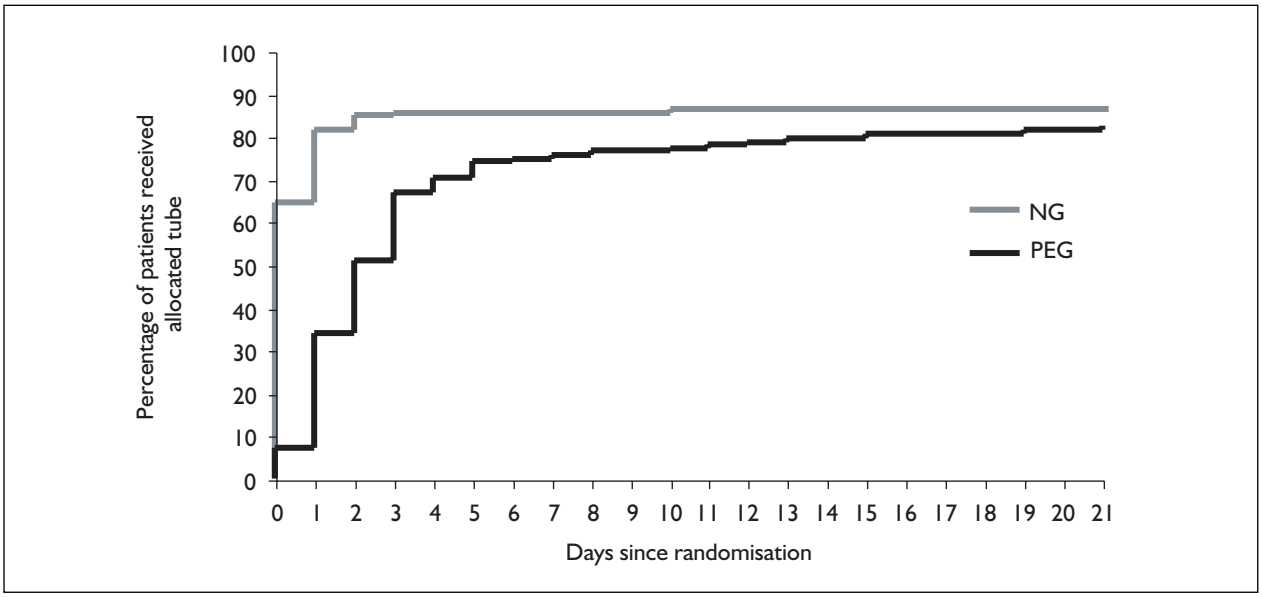

FIGURE 26 *Percentage of patients starting their allocated method of feeding during the first month after randomisation in Trial 3*

The reasons for non-compliance included the death of the patient before tube feeding could be started, improvement in swallowing ability, change of mind by staff, patient or relative or simple errors in recording the allocated treatment. Tube feeding was often delayed because of the difficulty in accessing early PEG.

Figure 27 shows the percentage of patients receiving enteral tube feeding via PEG or NG or other feeding (either none, parenteral fluids or oral) following randomisation to hospital discharge and the percentage discharged or dying during the first 6 months after recruitment in each treatment group. The duration of PEG feeding was considerably longer than NG feeding [median 28 days (IQR 13–59) compared with 7 days (IQR 2–18] and also the average time each tube stayed in place [median 27 days (IQR 13–59) compared with 3 days (IQR 1–7)]. The median number of PEGs was 1 (IQR 1) compared with two NGs (IQR 1–4, maximum 18).

Adverse events

Of the 155 deaths reported, 11 (7.1%) were attributed to the trial treatment by the responsible physician, three in the NG arm and eight in the PEG arm. Interestingly, events reported as attributable to trial treatment were all recorded in UK centres.

Causes of death

A total of 155 deaths were reported, of which 76 were in the NG arm and 79 in the PEG arm. The most common cause of death was pneumonia [36/76 (47.4%) in the NG group compared with 45/79 (57.0%) in the PEG group]. Causes of death are presented in *Table 29*.

Primary outcome

The sample size calculations were based on a dichotomous outcome – death or poor outcome (MRS 4–5) at follow-up. The two primary analyses are based on death or poor outcome and overall survival, subdivided by allocated treatment, irrespective of compliance.

The numbers and proportion of enrolled patients who died and the MRS of survivors in each treatment arm are given in *Table 30* (and graphically in *Figures 28* and *29*).

Allocation to PEG feeding was associated with a non-significant increase in the absolute risk of death of 1.0% (95% CI –10.0 to 11.9%; $p = 0.9$) but a borderline significant increase in the absolute risk of death or poor outcome of 7.8% (95% CI 0.0 to 15.5%, $p = 0.05$) (*Figure 30*). The effect of adjusting for any baseline imbalance in minimisation variables is shown in *Table 31*. There was no significant difference between the Kaplan–Meier survival curves (log-rank test, $p = 0.9$) (*Figure 31*).

Secondary outcomes

In-hospital complications

There was a statistically significant difference in the rate of gastrointestinal (GI) haemorrhages

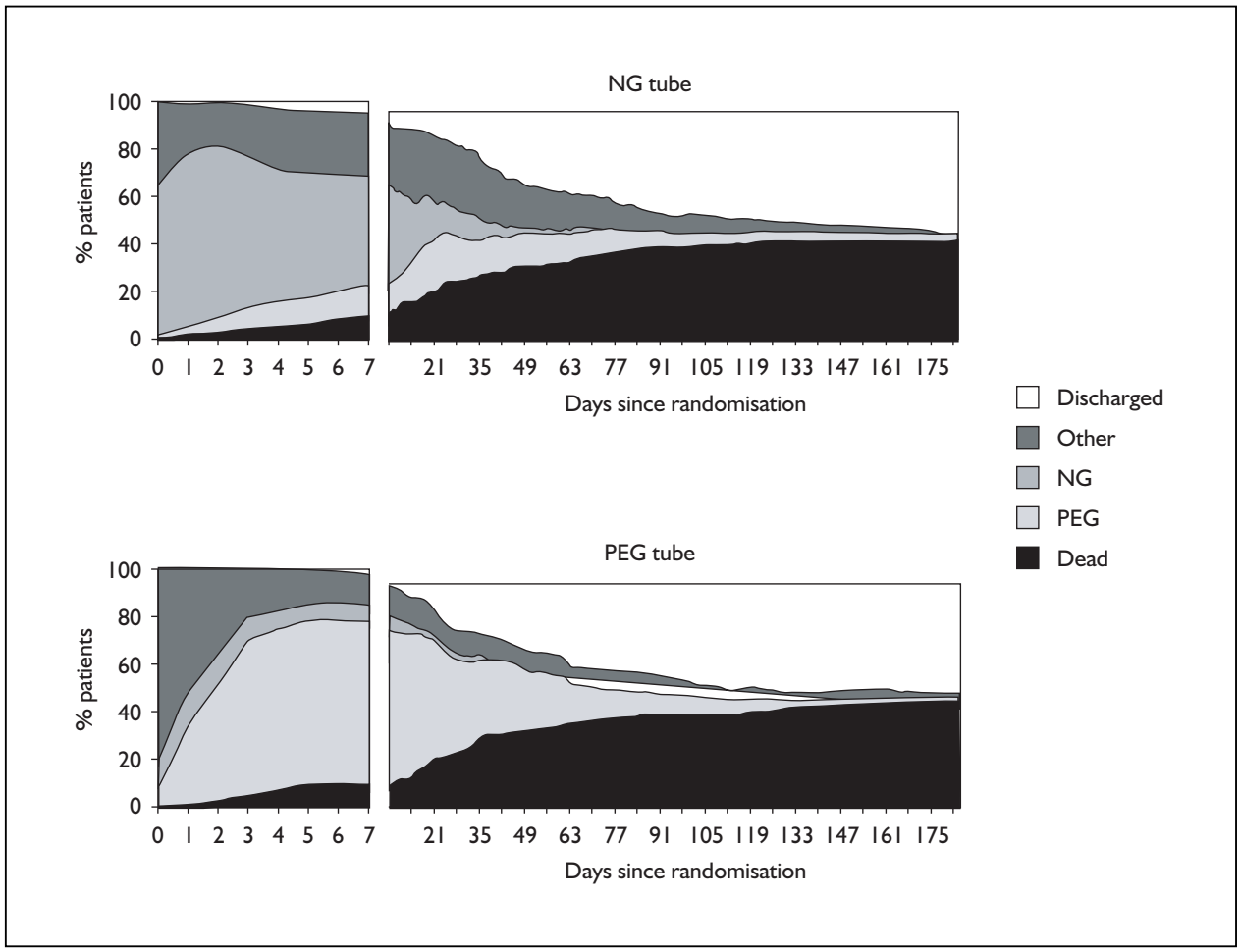

FIGURE 27 *Percentage of patients receiving enteral tube feeding via PEG or NG feeding or other feeding (none, parenteral fluids or oral) following randomisation to hospital discharge, the percentage discharged or dying in Trial 3. Note it includes death following discharge but does not show the proportion receiving tube feeding after discharge.*

TABLE 29 *Causes of death in Trial 3*

	NG tube	PEG tube	Total
Initial stroke	13 (17.1%)	15 (19.0%)	28 (18.1%)
Pneumonia	36 (47.4%)	45 (57.0%)	81 (52.3%)
Pulmonary embolism	0 (0%)	1 (1.3%)	1 (0.7%)
Recurrent stroke	8 (10.5%)	6 (7.6%)	14 (9.0%)
Coronary heart disease	5 (6.6%)	3 (3.8%)	8 (5.2%)
Other vascular	10 (13.2%)	5 (6.3%)	15 (9.7%)
Sudden death	1	0	1
Stroke/cerebrovascular disease	1	1	2
Acute coronary syndrome	1	1	2
GI haemorrhage	3	0	3
Cardiac failure	3	2	5
Peripheral	1	1	2
Other non-vascular	3 (4.0%)	4 (5.1%)	7 (4.5%)
Carcinoma	0	2	2
Probable vascular death	1	0	1
Sepsis	2	1	3
Renal failure	0	1	1
Missing	1 (1.3%)	0 (0%)	1 (0.7%)
Total	76	79	155

TABLE 30 *Primary outcome and death in Trial 3*

	NG tube		PEG tube		Risk difference (%)	
MRS Score	***n***	**%**	***n***	**%**	**Difference**	**95% CI**
0	1	0.6	2	1.2		
1	3	1.9	0	0		
2	6	3.8	7	4.3		
3	20	12.6	9	5.6		
4	12	7.6	8	4.9		
5	41	25.8	57	35.2		
Dead	76	47.8	79	48.8	1.0	–10.0 to 11.9
Unknown	0	0	0	0		
MRS 0–3	30	18.9	18	11.1		
MRS 4–5	53	33.3	65	40.1		
Dead or MRS 4–5	129	81.1	144	88.9	7.8	–0.0 to 15.5
Total	159		162			

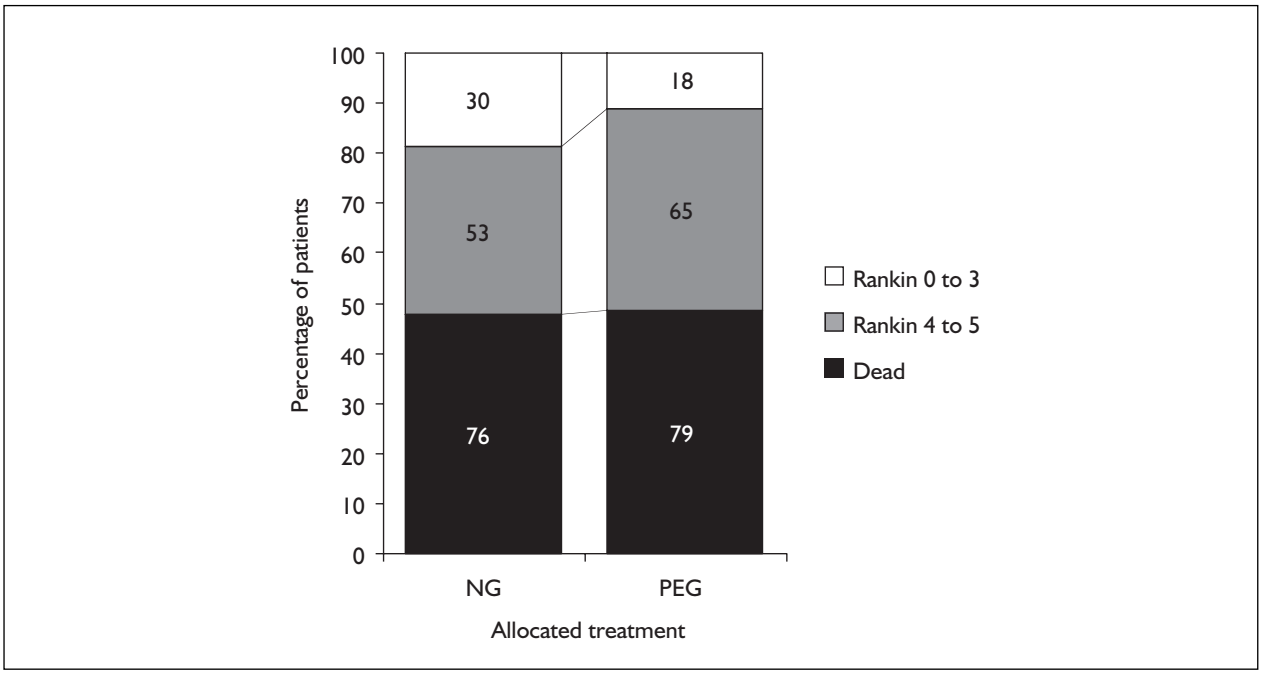

FIGURE 28 *Proportion of patients in each treatment group with primary outcomes in Trial 3. Patients with missing outcomes have been omitted as there are too few of them to show up.*

(bleeds) between treatment groups [18/159 (11.3%) in the NG group compared with 5/162 (3.1%) in the PEG group ($p = 0.005$)].

In the 18 allocated NGs, only seven bleeds occurred while an NG was *in situ*, four occurred after an NG had been removed and seven occurred while a PEG was *in situ*. Three bleeds were fatal, four were minor and it was unclear in the rest. Thirteen bleeds were from the upper GI tract and in the remainder it was unclear. The source of bleeding was duodenal ulcer (three), PEG site (one), oesophagitis (one), cancer (one), erosions (one) and unknown (11). In the five allocated PEG, three bleeds occurred with a PEG *in situ* and two with no tube. One bleed was fatal and two were major. Three were definitely from the upper GI tract and one from the lower GI tract and in the other it was uncertain. One upper GI bleed arose from a duodenal ulcer and in the remainder the source of bleeding was unclear.

Pneumonia and urinary infections were the commonest reported complications [115/321 (35.8%) in the NG group and 38/321 (11.8%) in the PEG group]. Interestingly, more patients

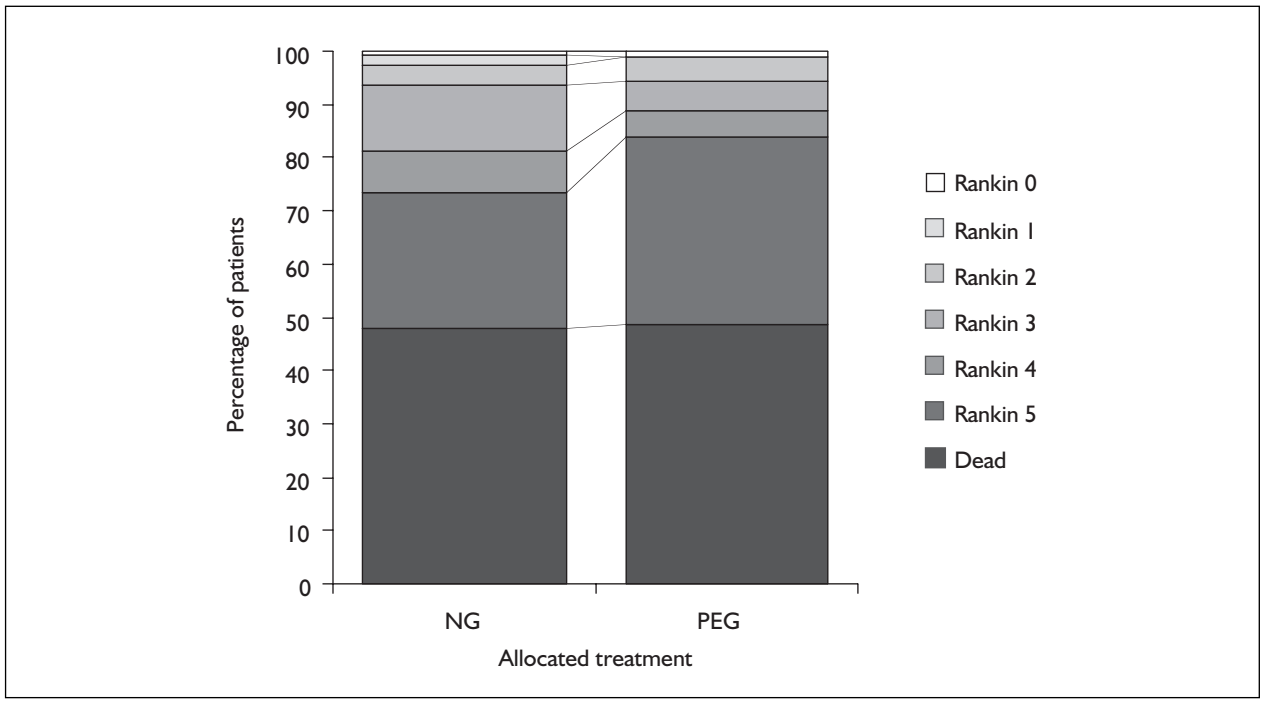

FIGURE 29 *Percentage of patients with each MRS at follow-up in each treatment group in Trial 3*

Outcome	PEG *n*/*N* (%)	NG *n*/*N* (%)	Risk difference (95% CI)	*p*-Value
Modified Rankin 4–6 v ersus 0–3	144/162 (88.9%)	129/159 (81.1%)	0.078 (–0.0002 to +0.155)	0.0504
Death	79/162 (48.8%)	76/159 (47.8%)	0.010 (–0.100 to +0.119)	0.862

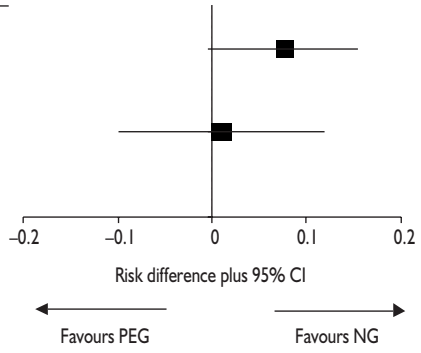

FIGURE 30 *Risk ratios comparing the primary outcomes of the two treatment groups in Trial 3*

allocated to PEG suffered pressure sores than those allocated NG [12/162 (74.4%) versus 4/159 (2.5%); $p = 0.0356$)]. However, these data on complications need to be interpreted with caution because of the lack of blinding to allocated treatment and the large number of statistical comparisons made and because it was not feasible to have local source data verified for the occurrence of complications. *Table 32* shows details of all complications recorded.

Length of hospital stay and discharge destination

LOS was available for all patients with a median LOS of 37 days in the NG group (IQR 17–76, mean 53, SD 52) and 34 days in the PEG group (IQR 17–66, mean 55, SD 68) [difference of means –2.1 days (95% CI –15.5 to 11.3)]. Although there were no significant differences in the discharge destinations between the two groups, slightly more patients allocated NG were discharged home with a partner or relative compared with the PEG

TABLE 31 *Effect of adjusting for any baseline imbalance in minimisation variables in Trial 3*[a]

Outcome		OR	95% CI	*p*-Value
Dead or MRS 4–5	Unadjusted	1.860	0.99 to 3.50	0.050
	Adjusted	2.108	1.05 to 4.22	0.032
Dead	Unadjusted	1.039	0.67 to 1.61	0.862
	Adjusted	1.021	0.65 to 1.61	0.929

[a] This was not a prespecified analysis but is often recommended by trial statisticians.
[b] Adjusted analyses have been adjusted for variables from the minimisation algorithm: country (Italy, Singapore, New Zealand, UK, other), age (<75, >75 years), sex, probability of poor outcome (<0.8, >0.8) and nutritional status (normal, undernourished, overweight).

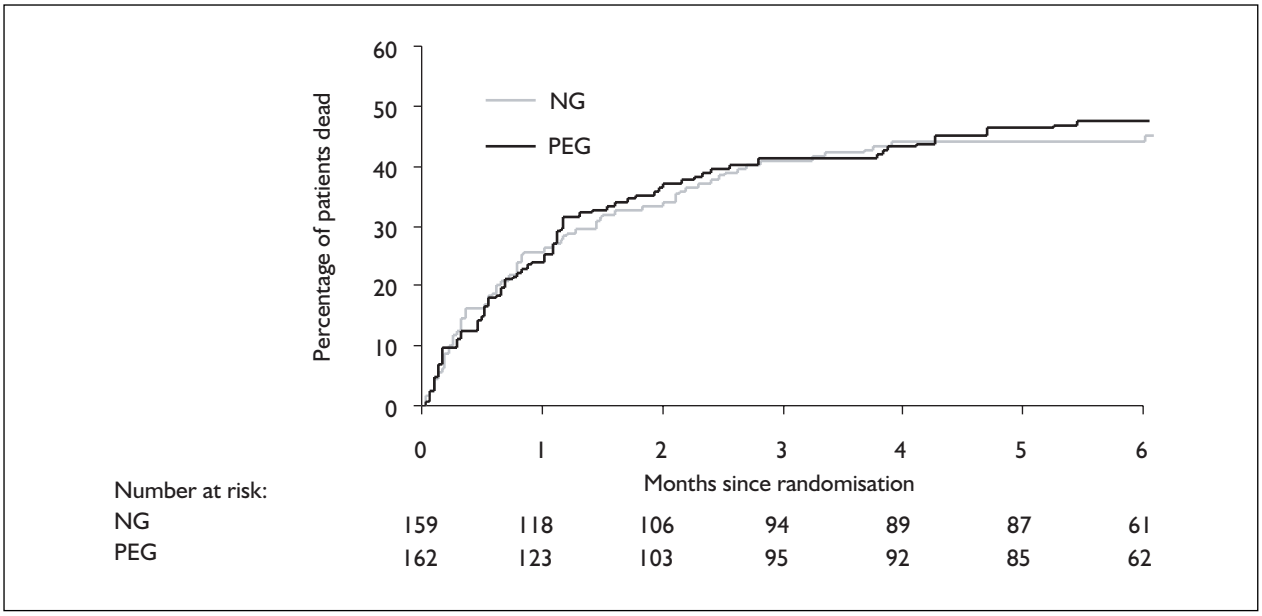

FIGURE 31 *Kaplan–Meier survival curves for the two treatment groups in Trial 3*

group where more were discharged to a nursing home (*Table 33*). There was also no significant difference in patients' residence at final follow-up (*Table 34*). Forty-three patients died between discharge and follow-up.

Feeding method at final follow-up

Table 35 shows the method of feeding in patients surviving to final follow-up. More patients in those allocated PEG were still being fed via a PEG at final follow up than in the NG group. This might either reflect less good recovery of swallow in this group or less effort to get the patient back on to oral feeding.

Quality of life (EUROQoL)

In Trial 3, QoL data were available in all but one patient (99.4%) in each arm. There were no major differences between treatment groups. The median utility, if dead patients were included, was 0.00 for both groups ($p = 0.12$) [difference of means (NG – PEG) +0.035 (95% CI –0.024 to +0.093)], but when dead patients were excluded the utility was better in the NG arm (0.08 versus –0.04; $p = 0.17$) (*Figure 32*). No differences were observed between the treatment groups in terms of mobility, self-care, usual activities, pain/discomfort and anxiety/depression. *Table 36* shows these data.

Subgroup analyses

The primary outcomes subdivided by baseline nutritional status and tertiles of predicted stroke outcome are shown in *Figure 33*. There was no significant heterogeneity of treatment effect between subgroups.

TABLE 32 *Secondary outcomes – in-hospital complications in Trial 3*

	Outcome	NG tube	PEG tube	Total	Log-rank *p*-Value
Randomised		159	162	321	
No discharge form		0	0	0	
Data available		159	162	321	
Recurrent stroke	Yes	6 (3.8%)	6 (3.7%)	12 (3.7%)	
	No	153 (96.2%)	156 (96.3%)	309 (96.3%)	>0.9
Neurological worsening	Yes	18 (11.3%)	12 (7.4%)	30 (9.4%)	
	No	141 (88.7%)	150 (92.6%)	291 (90.7%)	0.21
Pneumonia	Yes	59 (37.1%)	56 (34.6%)	115 (35.8%)	
	No	100 (62.9%)	105 (64.8%)	205 (63.9%)	0.64
	Yes but date?	0 (0%)	1 (0.6%)	1 (0.3%)	
Pulmonary embolism	Yes	1 (0.6%)	4 (2.5%)	5 (1.6%)	
	No	158 (99.4%)	158 (97.5%)	316 (98.4%)	0.19
Deep-vein thrombosis	Yes	3 (1.9%)	2 (1.2%)	5 (1.6%)	
	No	156 (98.1%)	160 (98.8%)	316 (98.4%)	0.65
Pressure sores	Yes	4 (2.5%)	12 (7.4%)	16 (5.0%)	
	No	155 (97.5%)	150 (92.6%)	305 (95.0%)	0.0356
GI haemorrhage	Yes	18 (11.3%)	5 (3.1%)	23 (7.2%)	
	No	141 (88.7%)	157 (96.9%)	298 (92.8%)	0.0050
UTI/cystitis including MRSA	Yes	22 (13.8%)	16 (9.9%)	38 (11.8%)	
	No	137 (86.2%)	146 (90.1%)	283 (88.2%)	0.30
PEG site including MRSA	Yes	10 (6.3%)	12 (7.4%)	22 (6.9%)	
	Yes but date?	1 (0.6%)	6 (3.7%)	7 (2.2%)	0.24[c]
	No	148 (93.1%)	144 (88.9%)	292 (91.0%)	
Other infections[a]	Yes	14 (8.8%)	12 (7.4%)	26 (8.1%)	
	No	145 (91.2%)	150 (92.6%)	295 (91.9%)	0.62
Diarrhoea	Yes	3 (1.9%)	4 (2.5%)	7 (2.2%)	
	Yes but date?	2 (1.3%)	2 (1.2%)	4 (1.3%)	>0.9[c]
	No	154 (96.9%)	156 (96.3%)	310 (96.6%)	
Acute coronary/cardiac arrest	Yes	6 (3.8%)	5 (3.1%)	11 (3.4%)	
	No	153 (96.2%)	157 (96.9%)	310 (96.6%)	0.77
Other medical problems[b]	Yes	16 (10.1%)	18 (11.1%)	34 (10.6%)	
	Yes but date?	3 (1.9%)	2 (1.2%)	5 (1.6%)	>0.9[c]
	No	140 (88.1%)	142 (87.7%)	282 (87.9%)	

[a] 'Other' includes all categories of infections that were experienced by ⩽10 patients (including infections of skin, eye, mouth, bile, MRSA infections, *C. difficile* infections, infections of known origin, infections of unknown origin, other infections).

[b] 'Other' includes all other medical problems that were experienced by ⩽10 patients (including MRSA colonisation, haemorrhage, hyper-/hypoglycaemia, neurological condition, renal/urinary problem, skeleton/joint/trauma, carcinoma, lung/respiratory, gastric/bowel, anaemia, gout, fracture, benign tumour, psychiatric, peripheral vascular disease, cardiac failure, cardiac rhythm disturbance, epistaxis).

[c] These are from a Fisher's exact test. There were too many missing data to use a log-rank test.

TABLE 33 *Discharge destination in Trial 3*

	NG tube	PEG tube	Total
Randomised	159	162	321
Own home alone	4 (2.5%)	4 (2.5%)	8 (2.5%)
At home, with partner/relative	35 (22.0%)	27 (16.7%)	62 (19.3%)
Relative's home	1 (0.6%)	1 (0.6%)	2 (0.6%)
Residential home	4 (2.5%)	3 (1.9%)	7 (2.2%)
Nursing home	28 (17.6%)	37 (22.8%)	65 (20.3%)
Other hospital	28 (17.6%)	23 (14.2%)	51 (15.9%)
Other	5 (3.1%)	8 (4.9%)	13 (4.1%)
Specialist ward	1	2	3
Hospital	0	1	1
Rehab/nursing home	4	4	8
Own home/sheltered housing	0	1	1
Not discharged from hospital	1 (0.6%)	0 (0%)	1 (0.3%)
Dead	53 (33.3%)	59 (36.4%)	112 (34.9%)
No discharge form	0 (0%)	0 (0%)	0 (0%)

TABLE 34 *Residence at follow-up in Trial 3*

Residence	NG tube	PEG tube	Total
Randomised	159	162	321
Own home alone	3 (1.9%)	4 (2.5%)	7 (2.2%)
Own/relative's home with partner/relative	37 (23.3%)	31 (19.1%)	68 (21.2%)
Residential home	3 (1.9%)	7 (4.3%)	10 (3.1%)
Nursing home	29 (18.2%)	31 (19.1%)	60 (18.7%)
Alive, not in hospital, but otherwise unknown	0 (0%)	0 (0%)	0 (0%)
Hospital	11 (6.9%)	10 (6.2%)	21 (6.5%)
Dead	76 (47.8%)	79 (48.8%)	155 (48.3%)
No follow-up	0 (0%)	0 (0%)	0 (0%)

TABLE 35 *Method of feeding at final follow-up in Trial 3*

Method	NG tube	PEG tube	Total
Randomised	159	162	321
Normal feeding	61 (38.4%)	47 (29.0%)	108 (33.6%)
NG tube	3 (1.9%)	2 (1.2%)	5 (1.6%)
PEG tube	19 (12.0%)	34 (21.0%)	53 (16.5%)
Alive, but method unknown	0 (0%)	0 (0%)	0 (0%)
Dead	76 (47.8%)	79 (48.8%)	155 (48.3%)
No follow-up	0 (0%)	0 (0%)	0 (0%)

TABLE 36 *Quality of life (EuroQOL) at final follow-up in Trial 3*

	NG tube	PEG tube	Total
	159	162	321
Mobility			
No problems	12 (7.6%)	9 (5.6%)	21 (6.5%)
Some problems	34 (21.4%)	26 (16.1%)	60 (18.7%)
Confined to bed	37 (23.3%)	48 (29.6%)	85 (26.5%)
Alive, data unknown	0 (0%)	0 (0%)	0 (0%)
Dead	76 (47.8%)	79 (48.8%)	155 (48.3%)
No follow-up	0 (0%)	0 (0%)	0 (0%)
Self care			
No problems	11 (6.9%)	8 (4.9%)	19 (5.9%)
Some problems	23 (14.5%)	21 (13.0%)	44 (13.7%)
Unable	48 (30.2%)	54 (33.3%)	102 (31.8%)
Alive, data unknown	1 (0.6%)	0 (0%)	1 (0.3%)
Dead	76 (47.8%)	79 (48.8%)	155 (48.3%)
No follow-up	0 (0%)	0 (0%)	0 (0%)
Usual activities			
No problems	7 (4.4%)	2 (1.2%)	9 (2.8%)
Some problems	16 (10.1%)	14 (8.6%)	30 (9.4%)
Unable	60 (37.7%)	66 (40.7%)	126 (39.3%)
Alive, data unknown	0 (0%)	1 (0.6%)	1 (0.3%)
Dead	76 (47.8%)	79 (48.8%)	155 (48.3%)
No follow-up	0 (0%)	0 (0%)	0 (0%)
Pain/discomfort			
None	31 (19.5%)	26 (16.1%)	57 (17.8%)
Moderate	45 (28.3%)	50 (30.9%)	95 (29.6%)
Extreme	7 (4.4%)	7 (4.3%)	14 (4.4%)
Alive, data unknown	0 (0%)	0 (0%)	0 (0%)
Dead	76 (47.8%)	79 (48.8%)	155 (48.3%)
No follow-up	0 (0%)	0 (0%)	0 (0%)
Anxiety/depression			
None	26 (16.4%)	17 (10.5%)	43 (13.4%)
Moderate	42 (26.4%)	58 (35.8%)	100 (31.2%)
Extreme	14 (8.8%)	8 (4.9%)	22 (6.9%)
Alive, data unknown	1 (0.6%)	0 (0%)	1 (0.3%)
Dead	76 (47.8%)	79 (48.8%)	155 (48.3%)
No follow-up	0 (0%)	0 (0%)	0 (0%)

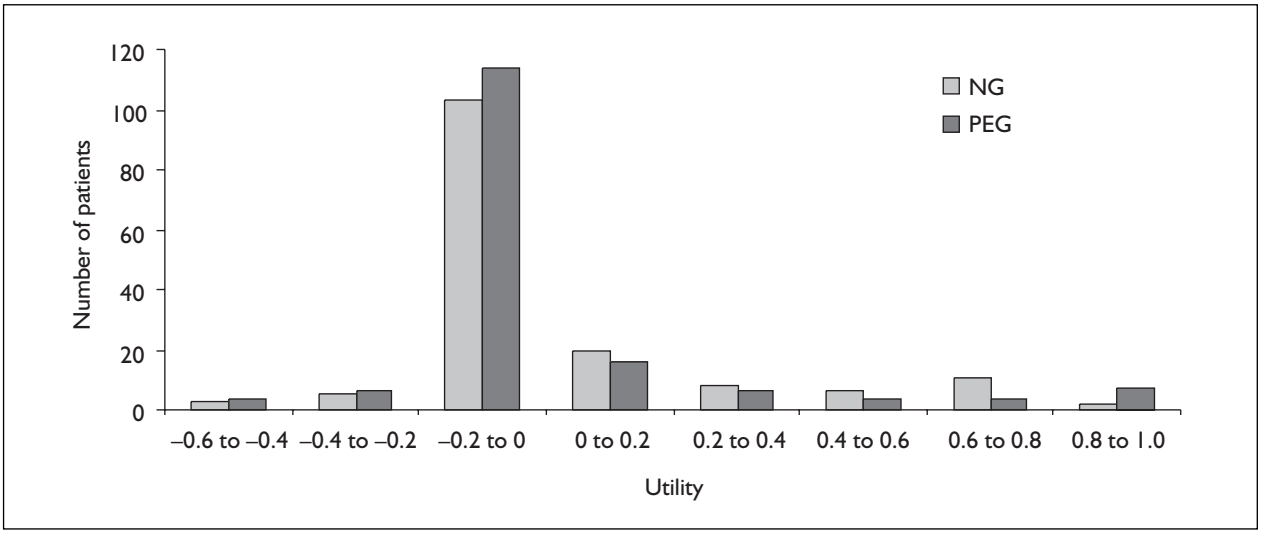

FIGURE 32 *Distribution of utilities (based on EuroQol) for the two treatment groups in Trial 3*

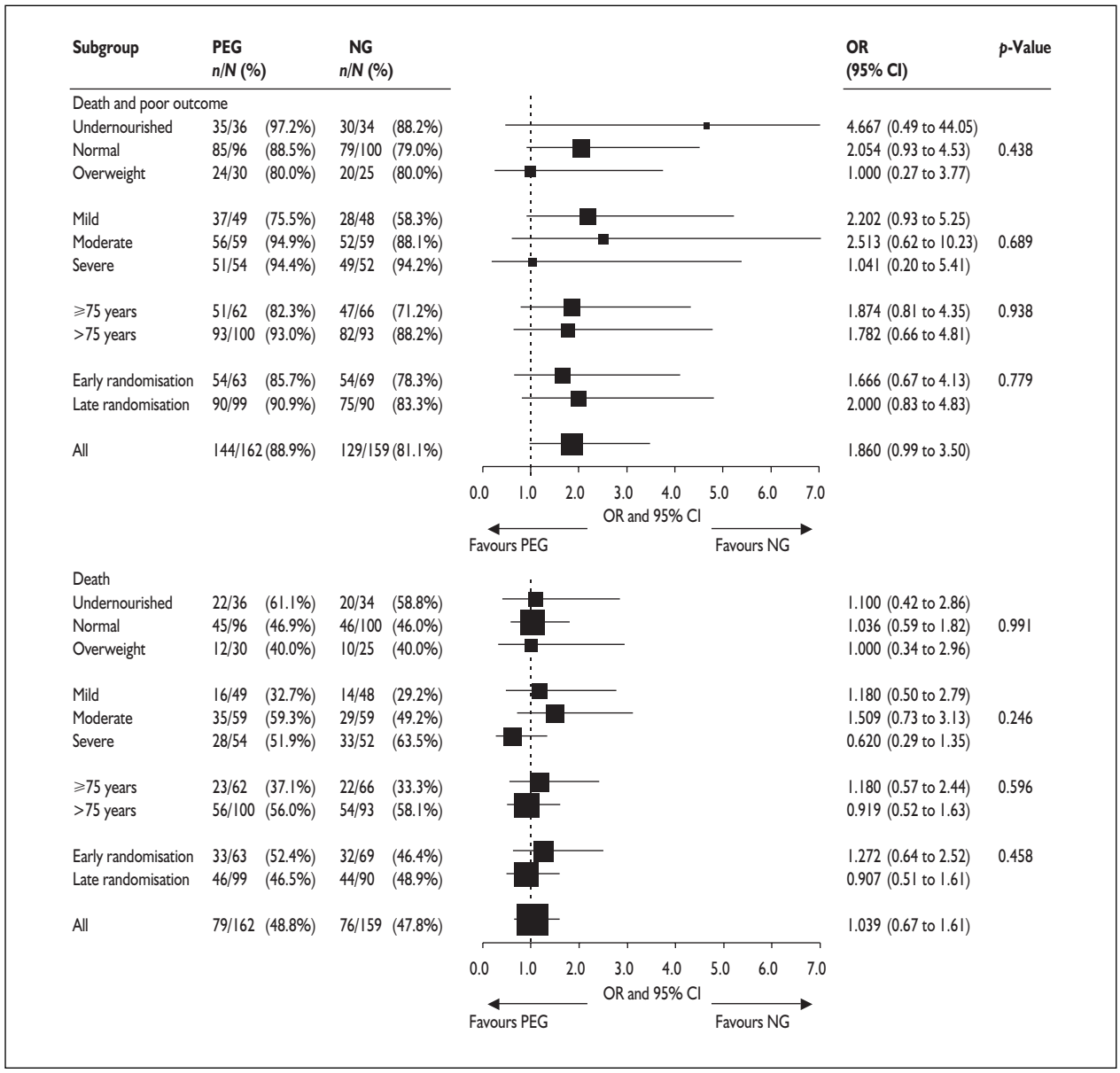

FIGURE 33 *Effect of NG tube feeding versus PEG tube feeding on both primary outcomes subdivided by baseline characteristics in Trial 3. Results are expressed as OR and 95% CI.*

Chapter 5

Health economic considerations

The trial design integrated measurement of survival, HRQoL and the use of hospital inpatient services. These trial outcomes allowed consideration of the primary health and resource consequences following different feeding policies for stroke patients. All patients enrolled in the trials were included in the assessment of health and resource effects. All analyses were by ITT using the perspective of the individual patient for HRQoL and the hospital for resource use.

Inpatient hospital use and cost

Patient-specific hospital use was measured using the LOS as an aggregate unit of services provided in the inpatient hospital setting. Total LOS was measured from the date of randomisation to the date of first hospital discharge after randomisation. Hence we included time spent in rehabilitation units if it formed part of the initial hospital admission. We did not count hospital admissions which occurred after the patient had been discharged to their normal or alternative residence. Hospital use was valued using the average cost per inpatient day using the Scottish system of hospital cost statistics and the NHS Information Authority[45] for spells, that is, the period from admission to discharge or death applied to hospital inpatient data from the Scottish Morbidity Record SMR01. Two Healthcare Resource Groupings (HRGs) for stroke were used: A22 (Non-transient Stroke or Cerebrovascular Accident >69 or with complications and/or co-morbidities) and A23 (Non-transient Stroke or Cerebrovascular Accident <70 without complications and/or co-morbidities). The inpatient hospital cost per day was £223 (A22) and £216 (A23). All costs are reported on the Scottish price base of financial year 2002–3 (NHS National Services Scotland).[46] No information was collected on centre-specific resource use or costs in the trials. We were unable to obtain information on any variation in the intensity of service use within a hospital spell or centre-specific resource costs for individual procedures or items of service. Undiscounted costs are reported. Although costs were recorded over the interval from randomisation to the time of follow-up, discounting costs incurred within the follow-up time frame at conventional rates of 3–6% would have very little effect on the magnitude of cost estimates as most of the costs were incurred within 1 year of stroke onset, admission and randomisation.

Survival and health-related quality of life

Cost-effectiveness analyses often use quality-adjusted life-years (QALYs) to summarise changes in survival and changes in HRQoL. In FOOD we were able to compare the mean survival times and calculated point estimates (and corresponding CIs) of the difference in life (days). We did collect EuroQoL at follow-up which enabled us to calculate the effects of different feeding policies on utility values. However, like many trials in stroke, using a utility scale such as EuroQoL to estimate HRQoL at baseline is problematic. Without a baseline EuroQoL we were unable to estimate the change in EuroQoL, and hence QALYs, between the time of randomisation and follow-up.

We intended to estimate cost-effectiveness acceptability curves[47] or net benefit statistics for the different feeding policies. This general approach requires an estimate of the difference in costs and difference in effects. Non-significant differences in costs and/or effects can prove difficult to analyse and interpret within this framework. Although over some ranges differences in cost-effectiveness might be observed, when the joint density is centred on zero, there may be no monetary values attached to the health outcome where a reasonable percentage of the joint density is cost-effective/cost-ineffective. In practice, given the negligible differences in both survival and HRQoL measures across the trial treatment groups, we chose to report the cost differences concurrently alongside the differences in survival and HRQoL outcomes in FOOD.

We have not allowed for any arbitrary differences in the cost per inpatient day or the cost of treatment for specific interventions (e.g. early tube or PEG) using deterministic sensitivity analyses, as we felt that the stochastic uncertainty around our

TABLE 37 *Trial 1 mean and quantile costs and cost differences (95% CI) (unadjusted)*

	Hospital cost per patient (£)[a]		Cost difference (£)[b]
	No supplements (n = 2001)	Supplements (n = 2012)	
Total hospital cost[c]			
Arithmetic mean	7,406 (6,967 to 7,845)	7,842 (7,376 to 8,307)	436 (–204 to 1,076)
Quantiles of the distribution			
20	1,561 (1,512 to 1,728)	1,561 (1,512 to 1,728)	0 (–235 to 235)
40	2,899 (2,676 to 3,024)	2,899 (2,808 to 3,122)	0 (–250 to 250)
50	3,791 (3,568 to 4,089)	3,839 (3,672 to 4,237)	97 (–257 to 451)
60	5,400 (4,906 to 6,021)	5,575 (5,129 to 6,181)	175 (–393 to 743)
80	11,150 (10,693 to 12,042)	12,265 (11,421 to 13,157)	1,115 (-6 to 2,236)

[a] UK £ 2002–3 values, undiscounted.
[b] Positive cost difference indicates that supplements are more costly than no supplements.
[c] From randomisation to end of follow-up.

cost estimates would encompass such assumptions. For example, increasing/decreasing the cost of hospital treatment by 10% for feeding policies where we might expect service use to be more/less resource intensive would have little material impact on the estimated cost differences.

Statistical analysis of inpatient hospital costs

Mean incremental costs

The full sample method was used to summarise the cumulative distribution of the inpatient hospital costs arising from the time of randomisation to follow-up using arithmetic mean costs observed for all patients. CIs for estimated untransformed arithmetic mean costs were estimated analytically and empirically using bootstrapping techniques[48] to check for the adequacy of the assumptions made regarding the normality of the cost distributions. We found that standard t-tests and t-test-based CIs were very similar to those based on the bootstrap.

Mean versus quantile treatment effects

We also considered heterogeneity in the impact of feeding policies on hospital costs and HRQoL by estimating quantile treatment effects (QTEs) across the distribution of total hospital costs and utility. This allowed a comparison of mean treatment effects with the treatment effects calculated at specific quantiles of the distributions to see whether the effects were uniform or concentrated amongst specific groups. The quantile regression model[49,50] provides an efficient way to examine the impact of treatment (and other covariates) on the location, scale and shape of the entire distribution of cost or other outcome variable of interest. Quantiles and their CIs are estimated with no assumptions about the underlying distribution. QTEs are based on a simultaneous quantile regression model for quintiles (20, 40, 60, 80) and the median (50).

For both mean treatment effects and QTEs, we calculated unadjusted and adjusted estimates using the covariates used in the trial minimisation algorithms: country, age, sex, probability of poor outcome and nutritional status. As the unadjusted and adjusted estimates were very similar, we only report the unadjusted results.

All health economic analyses reported in this section were conducted using Stata Statistical Software, release 8.[51]

Mean costs and cost differences

Table 37 presents unadjusted mean costs and cost differences for patients randomised to no

TABLE 38 *Trial 2 mean and quantile costs and cost differences (95% CI) (unadjusted)*

	Hospital cost per patient (£)[a]		Cost difference (£)[b]
	Avoid tube (*n* = 427)	**Early tube (*n* = 428)**	
Total hospital cost[c]			
Arithmetic mean	9,819 (8,780 to 10,857)	10,072 (8,864 to 11,279)	253 (–1,337 to 1,844)
Quantiles of the distribution			
20	2,453 (2,230 to 2,676)	2,230 (2,160 to 2,676)	–223 (–529 to 83)
40	4,237 (3,791 to 4,921)	4,460 (4,014 to 4,948)	223 (–573 to 1,020)
50	5,575 (5,088 to 6,467)	5,575 (5,004 to 6,244)	0 (–1,043 to 1,043)
60	7,760 (6,467 to 9,366)	7,359 (6,331 to 8,265)	–446 (–2,197 to 1,305)
80	15,922 (13,606 to 17,840)	15,164 (12,744 to 16,948)	–669 (–3,049 to 1,711)

[a] UK £ 2002–3 values, undiscounted.
[b] Positive cost difference indicates that early tube is more costly than avoid tube.
[c] From randomisation to end of follow-up.

supplements or supplements in Trial 1. The mean cost of hospital treatment was around £7624 for these patients with a slight cost increase of £436 (95% CI –204 to 1076) for patients randomised to supplements. This difference in mean costs of around 6% was not significant. The QTE ranged from £0 to £1115 with no significant differences in the costs of inpatient care following randomisation at these selected quantiles.

A similar pattern of cost differences emerged for patients in Trial 2. *Table 38* reports unadjusted mean costs and cost differences for early tube feeding versus avoid tube feeding for 1 week. The mean cost of hospital treatment is just under £10,000 for these patients with very little difference in costs (£253), equivalent to around 1 day in hospital. The QTE range is from –£669 to £223, suggesting that the cost distributions are very similar for both trial arms.

Table 39 reports unadjusted mean costs and cost differences for NG versus PEG. The average cost of hospital care for these patients has increased to £12,327 with a (insignificant) cost difference of £644 in favour of NG. The QTE ranges widely. For patients at the lower end of the cost distribution (below the median), the impact of PEG appears to be both increased and decreased costs, but again these differences are not significant.

These results on mean and quantile cost differences were confirmed for all trials when adjustments were made for country, age, sex, probability of poor outcome and nutritional status. Unadjusted and adjusted estimates were virtually identical and in no case did the cost differences become significant when adjusted models were used.

Survival and EuroQoL

Differences in survival and HRQoL measured by EuroQoL are reported in *Table 40*. Positive values indicate that supplements (Trial 1), early tube feeding (Trial 2) and PEG (Trial 3) are more effective compared with their respective alternatives. In general, these results mirror those reported for the distribution of costs. The trials do not appear to have any significant impact on mean survival days or the difference in survival days calculated at different points of the distribution. Although there is some weak evidence supporting a survival benefit from early tube feeding (Trial 2), this average difference of around 12 days is not significant.

The differences in utility measured at the time of follow-up using EuroQoL are very small and not significantly different from zero. This is true for

TABLE 39 *Trial 3 mean and quantile costs and cost differences (95% CI) (unadjusted)*

	Hospital cost per patient (£)[a]		Cost difference (£)[b]
	NG (*n* = 158)	**PEG (*n* = 162)**	
Total hospital cost[c]			
Arithmetic mean	12,001 (10,185 to 13,817)	12,645 (10,308 to 14,982)	644 (–2,314 to 3,602)
Quantiles of the distribution			
20	2,453 (1,976 to 4,069)	3,479 (2,497 to 4,683)	1,115 (–432 to 2,662)
40	6,823 (5,386 to 8,028)	5,798 (5,129 to 7,486)	–1,114 (-3,691 to 1,463)
50	8,251 (7,398 to 10,018)	7,805 (6,244 to 9,931)	–446 (–2,800 to 1,908)
60	10,927 (8,727 to 12,998)	10,481 (8,251 to 13,603)	–446 (–3,878 to 2,986)
80	18,122 (16,545 to 21,954)	18,509 (15,128 to 22,468)	0 (–4,294 to 4,294)

[a] UK £ 2002–3 values, undiscounted.
[b] Positive cost difference indicates that PEG is more costly than NG.
[c] From randomisation to end of follow-up.

TABLE 40 *Differences in survival and EuroQoL (95% CI) (unadjusted)*

	Trial 1[a]		Trial 2[a]		Trial 3[a]	
	Survival days[b] (*n* = 2004)	**EuroQoL[c] (*n* = 1986)**	**Survival days[b] (*n* = 429)**	**EuroQoL[c] (*n* = 421)**	**Survival days[b] (*n* = 159)**	**EuroQoL[c] (*n* = 158)**
Mean difference	–3 (–4 to 9)	–0.001 (–0.025 to 0.023)	12 (–6 to 29)	–0.013 (–0.053 to 0.028)	5 (–24 to 33)	–0.034 (–0.093 to 0.024)
Quantile differences						
20	0 (–1 to 1)	nc[d]	4 (–4 to 12)	–0.043 (–0.111 to 0.025)	2 (–18 to 22)	–0.123 (–0.249 to 0.003)
40	1 (–2 to 4)	0.013 (–0.039 to 0.065)	36 (–48 to 120)	nc	–4 (–101 to 83)	nc
50	–2 (–7 to 3)	nc	7 (–12 to 26)	nc	–6 (–64 to 52)	nc
60	–1 (–5 to 4)	0 (–0.019 to 0.019)	13 (1 to 25)	nc	1 (–14 to 16)	nc
80	–2 (–15 to 11)	0.016 (–0.006 to 0.038)	25 (–5 to 55)	0 (–0.104 to 0.104)	1 (–27 to 29)	–0.119 (–0.306 to 0.068)

[a] Positive values are in favour of supplement, early tube or NG in Trials 1, 2 and 3, respectively.
[b] From randomisation to end of follow-up.
[c] At time of follow-up.
[d] nc, not calculated as both the quantile value and the estimated quantile treatment effect are zero.

the mean difference and the QTE calculated across the EuroQoL distributions. The adjusted results for differences in survival and EuroQoL did not change these general findings based on the unadjusted analyses.

Discussion

The costs estimated in this pragmatic stroke trial accounted for the inpatient hospital spell(s) following randomisation up to the time of follow-up. It reflected contemporary utilisation of hospital inpatient services by patients allocated to one of the feeding policies in FOOD. Although we believe that our estimate of the differences in hospital costs between these alternative policies is robust, the absolute and relative differences are primarily a reflection of observed practice in trial centres between 1996 and 2003 and the specific resource unit costs applied in our study. Our estimate of the cost per day for stroke patients is very close to what we calculated in a previous disaggregated analysis of the cost of caring for stroke patients[52] and other recent reports that have applied unit costs in international stroke trials.[53] Both resource use and cost will vary across different healthcare systems and may change over time as novel interventions are adopted and a new pattern of service use is established.

Our results should be interpreted carefully against the background of comparisons of resource use over a short time horizon for small numbers of patients, particularly in Trial 3. This has the inevitable effect of making inferences less precise and reliable than we would like. In addition to the standard problems encountered when comparing distributions estimated with a (large) degree of imprecision, we have the attendant problem of censoring as we were unable to follow up patients beyond a relatively short period following randomisation.

This economic evaluation of feeding policies for stroke patients can be used to inform some of the arguments surrounding the choice of policy. It appears that supplements have little impact on either the distribution of resource costs or health effects. Early tube feeding may offer a slight survival advantage at little or no additional cost. Given the evidence on the primary trial outcomes, PEG may be not only less effective but also more costly when compared with NG.

Chapter 6

Updated relevant systematic reviews

Introduction

The results of randomised trials should wherever possible be placed into context by incorporating them into relevant systematic reviews. These should provide the least biased and most precise estimates of treatment effects. The problem here is the small sample sizes of previous trials and the lack of directly comparable trials with respect to the patient groups and outcomes. In this chapter we shall briefly present the meta-analyses resulting from our prospective collaboration with two groups of Cochrane Collaboration reviewers.

Methods

The methods of identifying relevant trials, selecting trials, extracting data and summarising data have been reported elsewhere.[25,54,55] These are similar for all the systematic reviews presented.

Trial 1

We updated, using previously described methods,[55] a published systematic review of randomised trials of oral supplements in elderly patients with medical problems to include the data from the FOOD trial and the other trials reported between 1966 and 2004.

Results

The results are summarised in *Figures 34* and *35*. In *Figure 34* we have grouped trials depending on their patient populations. Two trials included only patients with stroke whereas the remainder included elderly medical patients some of whom may have suffered a stroke. There was no statistically significant heterogeneity between the individual trials or between these groups. The results of the FOOD Trial 1 were far more conservative than those of Garriballa and colleagues, which had, in a trial of just 40 patients, shown a huge mortality benefit from oral supplements.[27]

In *Figure 35* we have divided trials into those which had only enrolled patients judged to be undernourished at baseline and those where patients were adequately nourished. Three trials including FOOD categorised the patients at baseline by their nutritional status and these we have included in each group. There appeared to be slightly larger benefits in those judged to be undernourished at baseline but there was no statistically significant heterogeneity between the two groups of trials.

In an attempt to assess the likelihood of our results being affected by publication bias, we produced a funnel plot (*Figure 36*).

Trial 2

Although there have been trials of NG tube feeding in various clinical situations and these have been summarised in a systematic review, we did not feel that there was enough in common to justify including the data from Trial 2 into this.[25] Trial 2 is the first reported RCT evaluating early tube feeding in stroke patients.

Trial 3

We updated, using previously described methods,[54] a published systematic review of randomised trials comparing NG and PEG feeding after stroke to include the data from the FOOD trial and the other trials reported between 1966 and 2004.

Results

We identified only three trials which we judged to be comparable. Norton and colleagues' trial randomised 30 stroke patients between PEG and NG tube feeding.[31] This indicated a large mortality advantage in favour of those fed via PEG. However, although the effect was statistically significant at the 5% level, it was based on just 10 outcomes and the CIs were very wide. Moreover, no baseline data were published to indicate whether randomisation had achieved reasonable balance of prognostic factors in the two treatment groups.

We included data from Bath and colleagues' pilot trial, which was terminated early.[54] Unfortunately, in this trial all patients in both treatment groups were categorised as having a poor functional outcome of death so it was uninformative with respect to our primary outcomes (death, 'death or MRS 4–5').

We also included data from the unpublished PEGASUS trial, which randomised 62 stroke

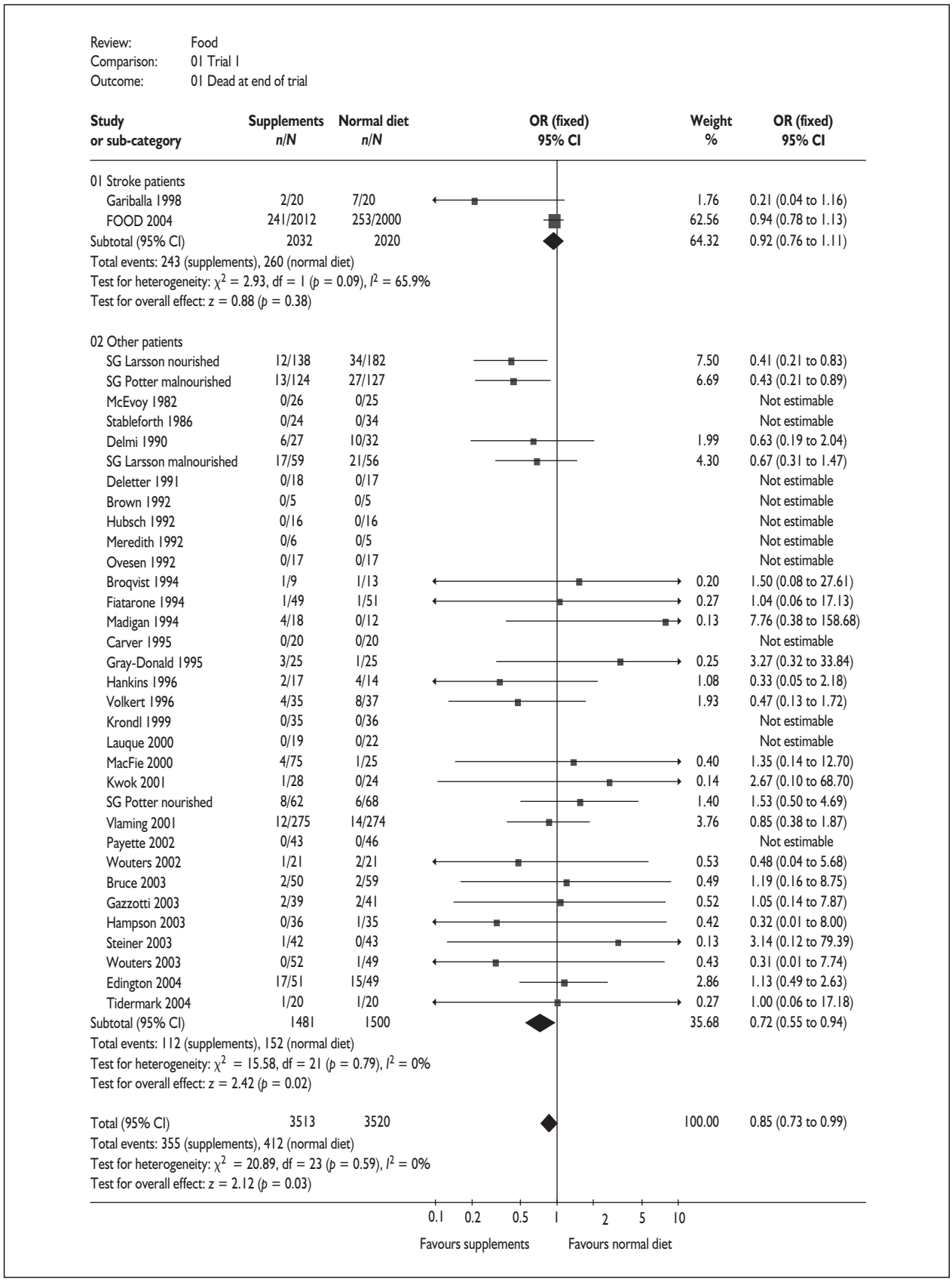

FIGURE 34 *A systematic review of the trials of oral supplementation amongst elderly medical patients (mean age >65 years), showing the effect on death by end of follow-up. The trials are subdivided by the nature of the baseline medical condition (purely stroke versus other conditions and mixed population which may have included some stroke patients). Effects are expressed as Peto OR, calculated with a fixed-effects model, with 95% CI. SG, subgroup; I^2, test for heterogeneity. References in Appendix 9.*

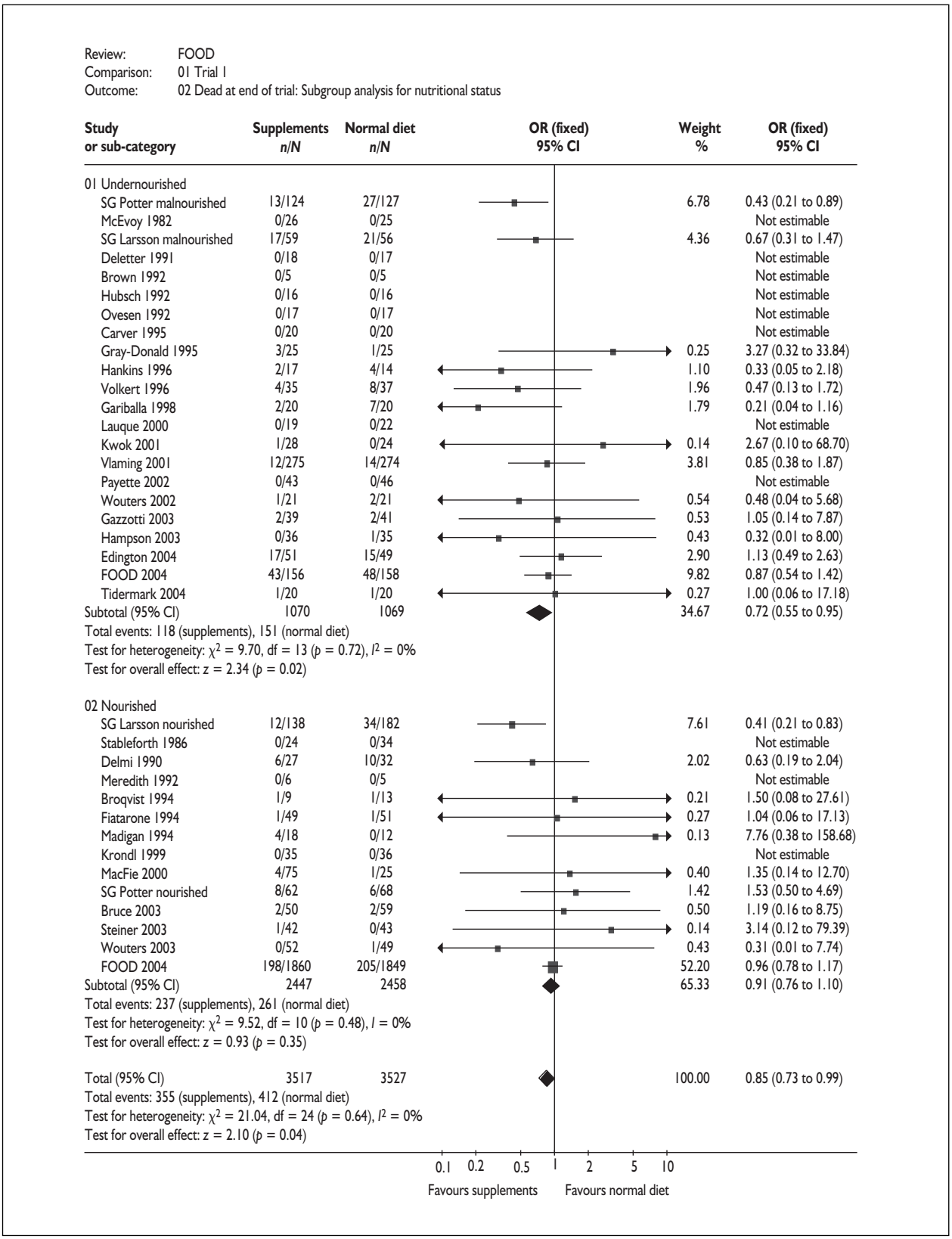

FIGURE 35 *A systematic review of the trials of oral supplementation amongst elderly medical patients (mean age >65 years), showing the effect on death by end of follow-up. The trials are subdivided by patients' baseline nutritional status. Most trials included in the undernourished included only patients judged to be undernourished at entry. We split the FOOD trial patients into those who were undernourished and those who were normal or overweight at baseline. The trials of Potter and Larsson separated those who were undernourished at baseline from the rest. Effects are expressed as Peto OR, calculated with a fixed-effects model, with 95% CI. SG, subgroup; I^2, test for heterogeneity. References in Appendix 9.*

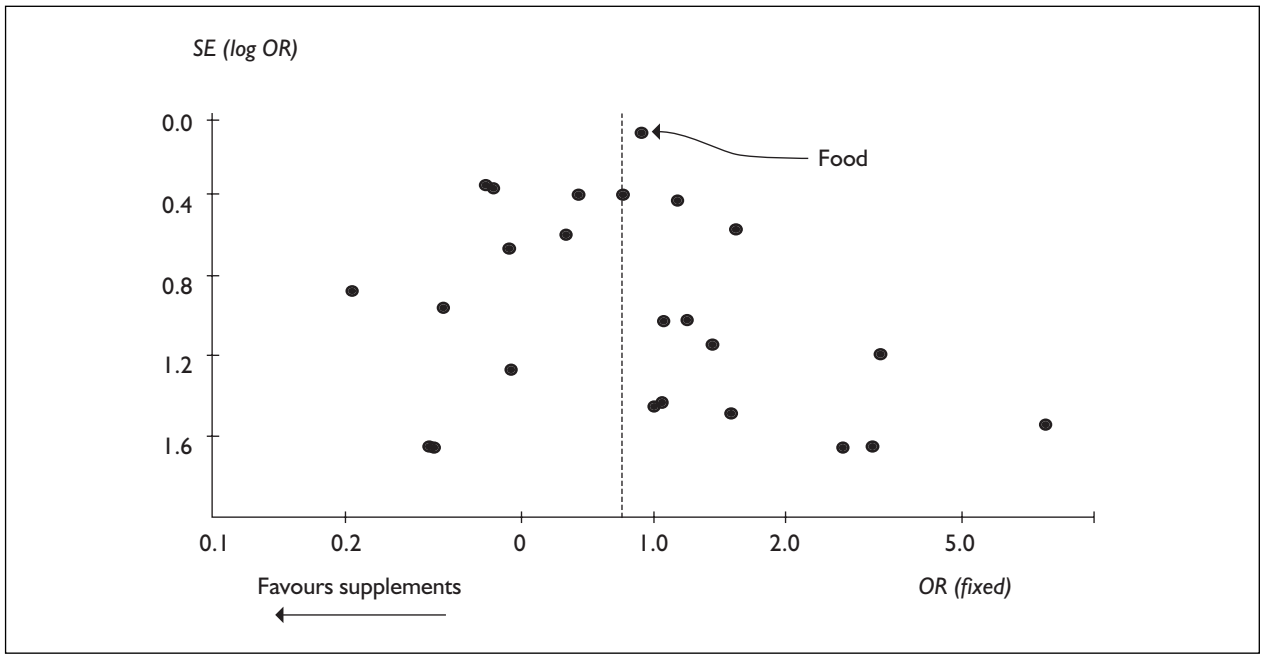

FIGURE 36 *Funnel plot of RCTs evaluating oral sip feeds in elderly medical patients. SE (log OR) for death by end of follow-up plotted against the OR derived from fixed-effects model.*

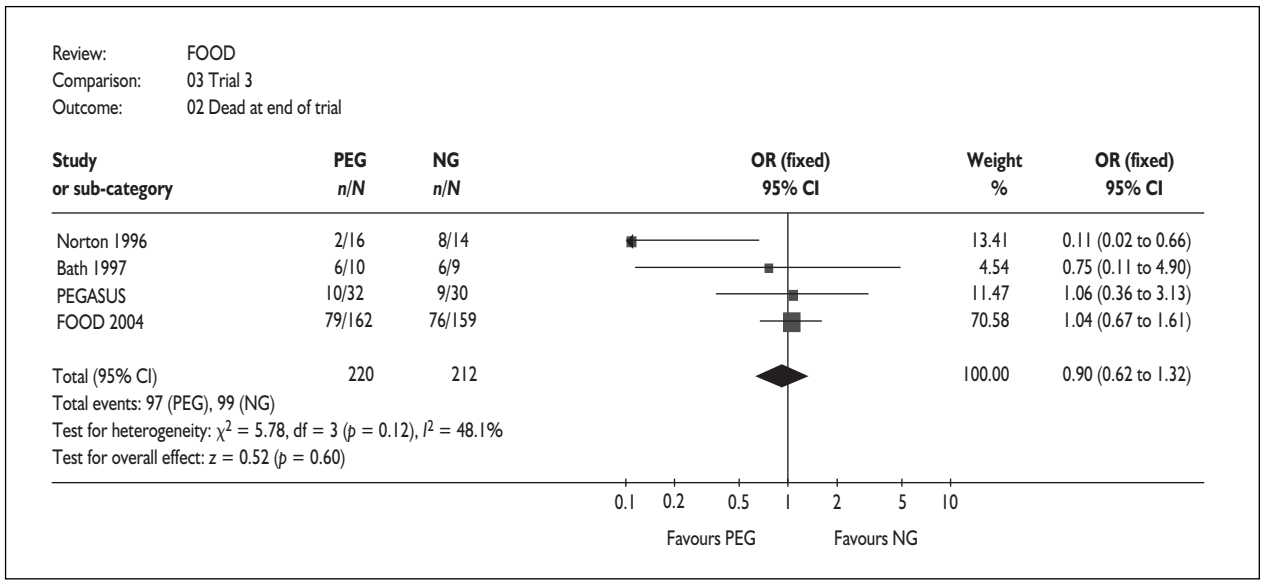

FIGURE 37 *A systematic review of the trials of NG versus PEG amongst stroke patients showing the effect on death by end of follow-up. Effects are expressed as Peto OR, calculated with a fixed-effects model, with 95% CI. I^2 = test for heterogeneity.*

patients between early PEG (between 5 and 10 days post-stroke) and delay PEG for at least 15 days since many of those allocated delay PEG were actually fed via an NG tube. Hence there were some similarities with Trial 3. Unfortunately, in the PEGASUS trial functional outcomes were only measured at hospital discharge and they were therefore confounded by different LOSs in the two treatment groups. In the PEGASUS trial, patients allocated PEG remained in hospital much longer than those allocated NG. However, case fatality was available for the patients enrolled in each group.

The results are summarised in *Figure 37*. The meta-analysis yielded an estimate that the OR for death was 0.88 (95% CI 0.59 to 1.33) in favour of PEG. This is not statistically significant; the CIs are wide and include the possibility of a large advantage or disadvantage with respect to survival

for PEG over NG. There is a moderate amount of heterogeneity (I^2 = 65%) between the trials – most clearly between that of Norton and colleagues and the others.

Discussion

We attempted to identify all the RCTs which have tested comparable interventions to those evaluated in the FOOD trials. We used fairly standard methods to search the literature and pool the data on effectiveness.

Systematic reviews should provide a more precise estimate of any treatment effect because they include outcome data on more patients than individual trials. They may not provide a precise estimate if the trials are too heterogeneous in the types of subjects enrolled, the interventions used or the timing and methods of measuring outcome. They may also provide biased estimates if there is publication bias or if the methodology of the individual trials was not rigorous.[56]

We formally evaluated the likelihood of publication bias in the systematic review of oral sip feeds for elderly medical patients. The funnel plot (*Figure 36*) suggested, if anything, that there were fewer small trials showing a large benefit from oral sip feeds. Based on this analysis, it would be unlikely that our estimates were overly optimistic because of some failure to identify small negative trials.

However, all of the trials identified, other than FOOD, were relatively small, single-centre trials. The quality of these trials varied considerably. In common with many other areas of medicine, the published reports of trial methods and results often omitted important information. This means that even if we avoided publication bias, our estimates may have been biased. Potential sources of bias in individual trials include:

- Foreknowledge of treatment allocations. It is not possible to know to what extent this was a problem without detailed information about the method of randomisation concealment and its actual conduct.
- Observer bias in assessing outcomes. In single-centre trials without central follow-up, it is often more difficult to achieve blinding of outcome measurement although in our meta-analysis the primary outcome was death by end of follow-up period, which should not be prone to observer bias.
- Lack of prespecified analyses. Many of these small trials did not publish prespecified sample sizes and recruitment targets or plans for interim analyses. This can lead to extreme estimates of effect if trials are stopped as a result of an interim analysis. Also, if many outcomes are measured but only those which provide positive results are reported, this will bias the estimates of effect. Sometimes by altering the statistical method or adjusting for baseline imbalance one can increase or decrease the statistical significance of the trial result.

The systematic review of oral sip feeds in elderly medical patients suggested that their use might decrease case fatality, although we could not confirm that this was the case specifically in stroke patients. Also, we could not exclude the possibility that the apparent overall benefit was due to biases within individual trials. There was a suggestion that those who were undernourished at baseline may gain greater benefit, but there was no statistically significant heterogeneity between the trials in undernourished and normally nourished patients.

The FOOD Trial 3 dominated the systematic review of trials comparing PEG and NG feeding. The overall estimate of effect on death was still fairly imprecise but indicated that the size of benefit seen in the first trial, reported by Norton and colleagues,[31] was unlikely. Unfortunately, because measures of functional outcome in the PEGASUS trial were obtained at hospital discharge, rather than at a fixed time after randomisation, we could not include their data in our review. They had major differences in LOS which confounded interpretation of their functional outcomes.

Chapter 7

Survey of feeding practices in the UK in 2003

Introduction

In 2003, we performed a postal survey of clinicians responsible for stroke services in the UK. Our purpose was to assess clinicians' current views about feeding stroke patients and to assess the likelihood that we could significantly increase the recruitment into FOOD by either enrolling new UK centres or by identifying opportunities to increase recruitment in existing centres. Such surveys may be a useful tool also to increase awareness of the trial. We had performed a similar survey in 2000 directed specifically at FOOD centres, both in the UK and abroad, to identify any barriers to recruitment. The results of both the 2000 and 2003 surveys were used to inform the steering group's decision to stop recruitment in July 2003.

The purpose of reporting the methods and results of the 2003 survey in this report is to provide a context into which the FOOD results will be set. This, along with the data presented in our third survey (Chapter 8), will provide the basis for our conclusions concerning the implication for the trials results for clinical practice and research.

Methods

We constructed a postal questionnaire which aimed to determine what feeding policies were being followed by UK stroke physicians, geriatricians and neurologists. We compiled a mailing list from our FOOD Trial collaborators' database, the membership of the British Association of Stroke Physicians and a list of stroke units provided by the Stroke Association.

TABLE 41 *Responses to the question 'How often do you insert a PEG tube without first attempting NG feeding?'*

	Number	%
Never	54	46
Rarely	45	38
Sometimes	14	12
Usually	4	3
Always	0	–
Missing	0	–

The questionnaire was posted to all those on the combined list. Non-responders were sent a further copy of the questionnaire with a covering letter. Data from completed questionnaires were entered into Excel and analysed with SAS.

Results

A total of 218 UK clinicians were surveyed. We received responses from 121 (56%), of whom 117 regularly cared for stroke patients. Of these, 106 responders (91%) were consultant physicians, nine were nurse specialists, one was a speech and language therapist and one was of unknown profession.

Our questionnaire included items relating to factors which might influence the practicality of delivering enteral tube feeding to stroke patients. We therefore asked about physical restraints which units might use to help maintain NG feeding. Fifty-nine (50%) respondents claimed that none were used, 16 (14%) admitted to using mittens and 18 (15%) tied, taped or sutured nasogastrics tubes in place. This question was not answered by 24 (21%).

In total, 111 respondents estimated that the median delay for having a PEG inserted from their request was 7 days (range 1–40, IQR 5–10 days). Six clinicians did not answer this question. We also asked how often they would consider inserting a PEG without first attempting NG feeding. The results are given in *Table 41*.

In the questionnaire, we used hypothetical cases to explore the clinicians' views about feeding stroke patients. The cases and their responses are summarised in *Tables 42* and *43*. We also asked whether they had written protocols in place in their unit. A total of 104 (89%) had a protocol for swallowing assessment and 69 (59%) had one for dietary assessments. Forty-eight (41%) had a written protocol for initiating tube feeding and 50 (43%) had one for PEG feeding.

TABLE 42 *Study 1. A previously well 80-year-old lady is admitted to your unit with an ischaemic stroke causing a severe left hemiparesis but no dysphagia. You expect her to require several weeks of hospital-based rehabilitation. Based on your bedside assessment of her nutritional status, please indicate (with a tick in a box on each line) how you would manage her.*

Nutritional status on admission	Normal diet	Normal diet and oral supplements	Uncertain and prepared to randomise between normal diet and oral supplements	Missing
Undernourished	6	92	16	3
Normal	68	11	35	3
Overweight	95	3	13	6

TABLE 43 *Study 2. A previously well 80-year-old lady is admitted to your unit with an ischaemic stroke causing a severe left hemiparesis but you expect her to survive with a reasonable quality of life. She fails an initial bedside swallowing assessment. Based on your bedside assessment of her nutritional status, please indicate (with a tick in a box on each line) how you would manage her.*

Nutritional status on admission	Initiate enteral tube feeding immediately	Hydrate with parenteral fluids and only consider tube feeding if dysphagia persists	Uncertain and prepared to randomise between immediate tube feeding and delay for at least 7 days	Missing
Undernourished	67	32	15	3
Normal	37	57	20	3
Overweight	32	55	25	5

If you would be prepared to hydrate with parenteral fluids and delay tube feeding, how many days would you be prepared to delay tube feeding for?

Nutritional status on admission	3	4	5	6	7	8	9	10	11	12	13	14	>14	Missing
Undernourished	15	4	3	0	7	0	0	0	0	0	0	0	0	3
Normal	22	3	9	1	16	0	0	1	0	0	0	1	0	4
Overweight	23	3	3	0	15	1	0	5	0	0	0	1	0	4

*Depending on the patient's nutritional status, what sort of tube would you **first** insert?*

Nutritional status on admission	NG tube	PEG tube	Uncertain and prepared to randomise between NG and PEG	Missing
Undernourished	27	1	4	0
Normal	50	1	6	0
Overweight	50	1	4	0

At what stage, assuming that her dysphagia persisted but NG feeding was tolerated would you insert a PEG tube, given your hospital's current PEG waiting time?

Nutritional status on admission	1–5 days	5–10 days	11–15 days	16–20 days	21–25 days	25–30 days	>30 days	Missing
Undernourished	0	8	11	5	1	2	2	3
Normal	0	15	20	11	2	3	3	3
Overweight	0	14	18	11	1	3	5	3

At what stage, assuming that her dysphagia persisted but NG feeding was tolerated, would you insert a PEG tube if you had immediate access to PEG insertion?

Nutritional status on admission	1–5 days	5–10 days	11–15 days	16–20 days	21–25 days	25–30 days	>30 days	Missing
Undernourished	1	10	10	3	2	1	0	3
Normal	1	20	19	8	2	2	3	2
Overweight	0	19	16	10	3	2	3	2

Discussion

It appeared from their responses that patients' baseline nutritional status was taken into account in determining the feeding policy chosen. In general, clinicians favoured more aggressive feeding in undernourished patients. They would more often give supplements in undernourished than normally nourished or overweight patients. Few clinicians considered using supplements to prevent undernutrition in those with normal nutritional status or who were overweight at baseline.

In dysphagic patients, clinicians would initiate tube feeding earlier in those judged to be undernourished, but very few clinicians were prepared to delay enteral tube feeding for more than 7 days whatever a patient's baseline nutritional status. Hence enrolment in Trial 2, where patients could be allocated to avoid tube feeding for at least 1 week, would be difficult. We were interested in the apparent variation in the use of physical restraints to help maintain enteral tube feeding.

The relatively poor access to early PEG and the reticence to consider a PEG without first trying an NG tube indicated that we would struggle to enrol large numbers of patients into Trial 3 where the protocol required a PEG to be inserted within 3 days of randomisation and in patients without prior NG. Most clinicians would choose to insert a PEG within 3 weeks in patients with persisting dysphagia.

Relatively few clinicians were uncertain enough to consider randomising patients into the appropriate FOOD trial. These data were influential in determining the steering committee's decision to halt recruitment on 20 July 2003 despite not attaining the original targets for the three trials.

Of course, these responses are those of responders and, given an overall response rate of only 56%, may not represent the view of all UK stroke physicians. Nonetheless, they are the responses of a considerable number. Also, the views were based on hypothetical situations which may not reflect actual practice. Anecdotally, our recruitment coordinator reported that there were often major delays in initiating supplements or enteral tube feeding despite the existence of local protocols urging early assessment and intervention. Local protocols were in wide use, despite not being based on reliable evidence. These could inhibit clinicians from enrolling patients into randomised trials.

These data need to be considered, alongside those of clinicians' estimates of the likely effects of the feeding policies tested in the FOOD trial (see Chapter 8), when considering the likely implications for clinical practice.

Chapter 8

A survey of senior clinicians' estimates of the likely effects of feeding policies on outcomes

The purpose of the FOOD Trial was to provide a more precise and unbiased estimate of the effect of different feeding policies for stroke patients. By identifying the best policies we hope to reduce the use of less effective ones and hence reduce variation in practice.

There are several complementary approaches one can take to altering clinical practice. These include:

- Disseminating the results of the trials widely to members of the multidisciplinary team who might influence decision-making around individual patients or stroke unit policies. In this regard, it is vital to ensure that the data are disseminated in a format which is accessible and interpretable by these team members. This will include efforts to educate people in the appropriate interpretation of trial results, writing papers for peer-reviewed journals, review articles and book chapters and presentations at meetings.
- Ensuring that the results of the trial are incorporated into relevant systematic reviews, such as those produced by the Cochrane Collaboration, since these are increasingly the route taken to accessing information about most effective practice.
- Ensuring that those responsible for formulating national stroke guidelines (e.g. SIGN) are aware of the data and take account of them in the guidelines.
- Encouraging clinicians to introduce protocols and integrated care pathways which reflect the evidence and the guidelines.
- Ensuring that where the data strongly suggest that one policy or practice is superior, standards are set for following that policy. For example, NHS Quality Improvement Scotland stipulates that all stroke patients should have access to a stroke unit.
- Putting in place audit systems to monitor the performance of stroke services in delivering specific aspects of care so that gaps between the standard and the actual performance can be identified and reduced.

Clinicians' practices are based on their own beliefs about the relative effectiveness of different feeding policies after stroke. If we wish to assess the extent to which we need to alter practice, then we need to know how these beliefs are distributed amongst stroke clinicians. The survey of clinicians described in Chapter 7 provides one indication of the prior beliefs of clinicians regarding the relative effectiveness of different feeding policies. Another way of assessing this is to ask clinicians directly to guess the direction and size of any treatment effects which would be detected by the trial. To this end, as an adjunct to the FOOD Trial, we carried out a survey of senior clinicians' estimates of the likely treatment effects.

These data should enable us to judge the extent to which our data confirmed or refuted the expectation of clinicians and this might determine the extent to which practice was likely to change in response to dissemination of the results. Of course, each individual clinician will have their own prior belief, based on their clinical experience and interpretation (informed or flawed) of available data. Assuming that one can make that clinician aware of the trial results by any or all of the methods described above, then it is hoped that one can encourage their beliefs to change towards those which are supported by the evidence and that these modified beliefs will lead to more effective practice.

Methods

We constructed a brief questionnaire which asked clinicians to estimate the absolute differences in the proportion of patients receiving our different feeding allocations who would have our primary outcomes (death or MRS 3–5 in Trial 1 and death or MRS 4–5 in Trials 2 and 3). We provided them with an estimate of the proportion of patients with the primary outcome across both treatment groups, which was based on an interim analysis of our data performed on 20 October 2003 after cessation of trial recruitment. In case clinicians were not familiar with expressing treatment effects in terms

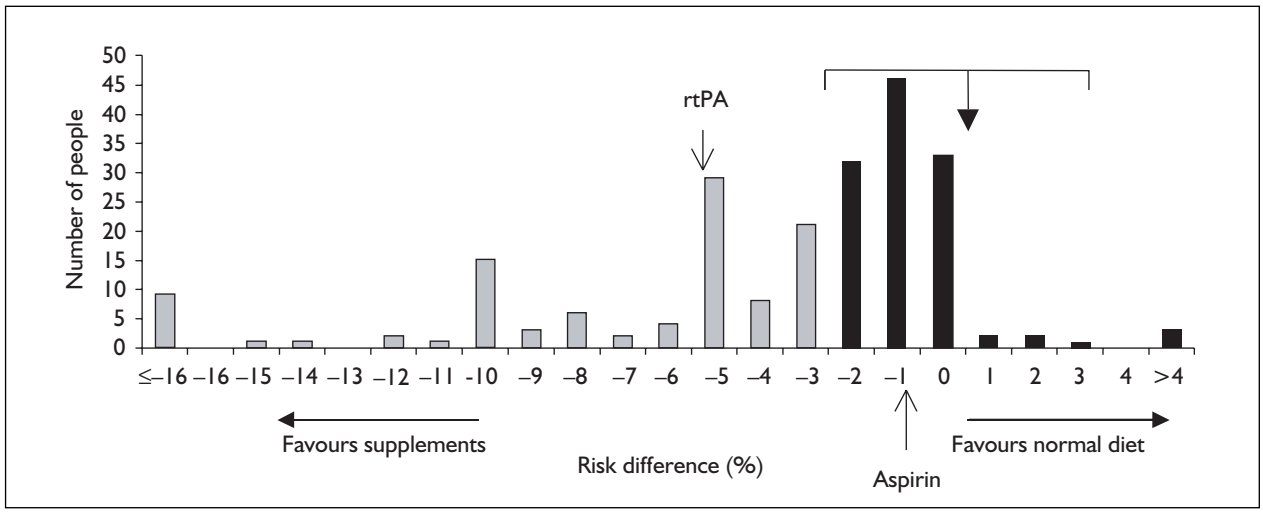

FIGURE 38 *Distribution of clinicians' estimates with respect to the likely size and direction of treatment effect in Trial 1 on death or MRS 3–5. We have superimposed the actual results (closed arrow) of the trial with the 95% CI (horizontal bar and black shading) and the point estimates (open arrows) for aspirin treatment from IST and CAST trials and rtPA from the Cochrane review.*

of absolute benefit, we provided two examples based on other stroke treatments with which they were likely to be familiar – first the effect of early aspirin in acute ischaemic stroke derived from the International Stroke Trial (IST)[57] and Chinese Acute Stroke Trial (CAST)[58] and second the effect of recombinant tissue plasminogen activator (rtPA) in acute ischaemic stroke derived from the Cochrane systematic review.[59]

We constructed a database of possible recipients of this survey. This included:

1. FOOD Trial collaborators.
2. Consultant members of the British Association of Stroke Physicians.
3. 'Clinicians in charge' of stroke units in the UK which appeared on a database provided by The Stroke Association. This did not always include names of individual clinicians.

Each person on the database was sent a questionnaire between November 2003 and February 2004, prior to the final analysis of the FOOD Trial data. Non-responders were sent at least one further questionnaire and this was supplemented by personal approaches (in person and by telephone) by the Principal Investigator to recipients known to him.

Data entry and analysis

Data from completed questionnaires were entered into an Excel spreadsheet. Responders were categorised as (1) medically qualified or not, (2) FOOD collaborator or not and (3) UK based or not. The distributions of estimates of effect size were plotted for each of the trials. Medians and IQRs were used to describe the distribution of estimates.

Results

In all, 420 persons were sent the questionnaire. We received 226 (53%) completed questionnaires – mostly from the UK and almost all from medically qualified individuals working at consultant level.

The distributions of estimates of absolute treatment effects for each of our trials are given in *Figures 38–40*. On these figures we have superimposed the point estimates with their 95% CIs from Trials 1, 2 and 3, respectively, and also added the point estimates provided to responders for aspirin and rtPA.

For Trial 1, the median of the clinicians' estimates for the effect on death or MRS 3–5 was –2.0%, IQR –0.6 to –5.0%, compared with an estimate of 0.7% (95% CI –2.3 to 3.8) from the trial itself. The majority of clinicians expected improved outcomes with oral supplements, the median effect size being about twice as large as that provided by 2 weeks of treatment with aspirin. Of course, the effect with respect to death alone was –0.7% (95% CI –2.7 to 1.4), which was in the same direction as expected by clinicians.

For Trial 2, the median of the clinicians' estimates was –3.8%, IQR –1.2 to –8.3%, compared with an

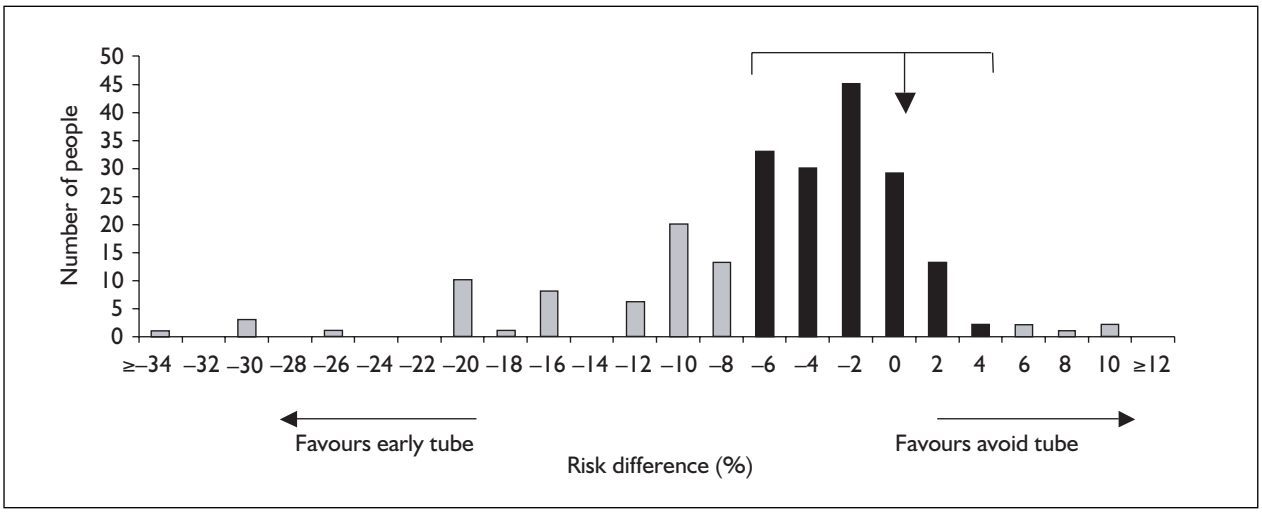

FIGURE 39 *Distribution of clinicians' estimates with respect to the likely size and direction of treatment effect in Trial 2 on death or MRS 4–5. We have superimposed the actual results (closed arrow) of the trial with the 95% CI (horizontal bar and black shading).*

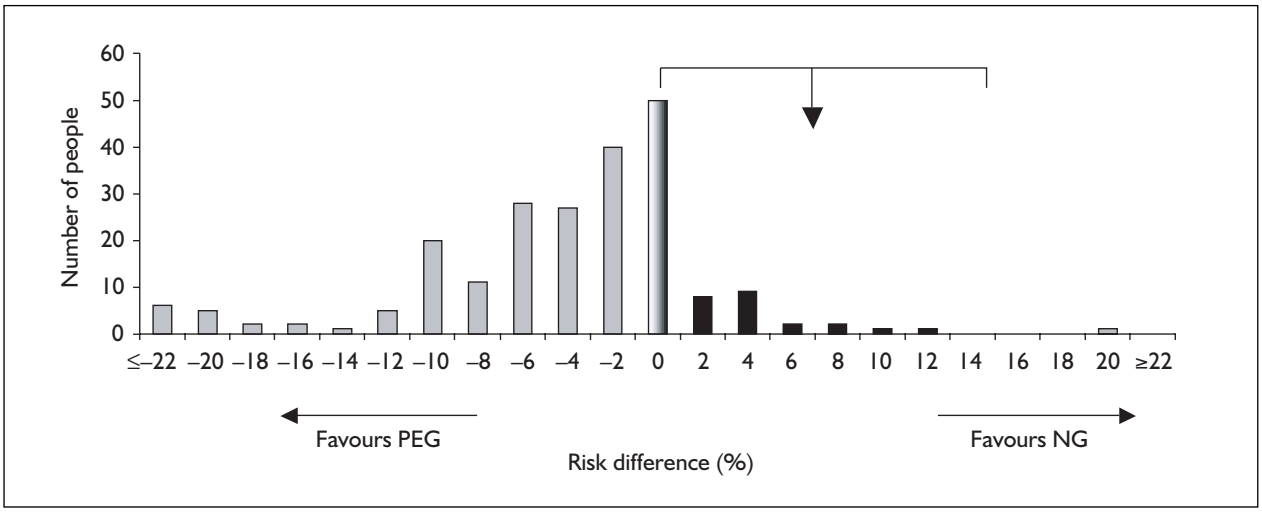

FIGURE 40 *Distribution of clinicians' estimates with respect to the likely size and direction of treatment effect in Trial 3 death or MRS 4–5. We have superimposed the actual results of the trial (closed arrow) with the 95% CI (horizontal bar and black shading).*

estimate of –1.2% (95% CI –6.6 to 4.2). Hence the clinicians' estimates on this occasion were in the same direction but with a larger benefit than that estimated by the trial, although less than the –5.8% (95% CI –12.5 to 0.8) seen in the trial for death alone.

For Trial 3, the median of the clinicians' estimates was –2.5%, IQR –0.2 to –6.4%, compared with an estimate of 7.8% (95% CI 0 to 15.5) from the trial itself. Hence the clinicians' expectations were of a moderate benefit from PEG whereas we demonstrated that such a benefit was very unlikely. The clinicians' expectations were more in line with our estimate of the effects on death alone, 1.0% (95% CI –10.0 to 11.9).

We also looked to see if there were differences between professional groups and countries, but the number of responses from non-doctors and other countries was small (*Table 44*).

Discussion

These data represent the views of a large number of mainly UK-based clinicians managing stroke patients. However, the response rate was moderate so they may not be truly representative of UK physicians in general. The responses from clinicians showed some digit preference, with more physicians estimating 0, 1, 5 and 10% differences. Some guessed that the treatments

TABLE 44 *Differences between professional groups and countries*

	Trial 1[a] (negative = favours supps)			Trial 2[b] (negative = favours early)			Trial 3[c] (negative = favours PEG)		
	n	Median	IQR	*n*	Median	IQR	*n*	Median	IQR
Overall	220	–2.0	–5.0 to –0.6	219	–3.8	–8.3 to –1.2	220	–2.5	–6.4 to –0.2
By job category[d]									
Doctor	216	–2.0	–5.0 to –0.6	215	–3.5	–8.3 to –1.0	217	–2.5	–6.4 to –0.2
Other[e]	4	–1.9	–2.9 to 1.6	4	–5.0	–9.5 to –3.4	3	–2.5	–3.5 to –1.2
By country[d]									
UK	202	–2.0	–5.0 to –0.5	202	–3.8	–8.3 to –1.0	202	–2.8	–6.4 to –0.2
Italy	6	–2.3	–6.2 to –0.5	6	–2.3	–9.0 to –1.1	6	–0.1	–8.3 to 1.8
Other[f]	12	–2.6	–4.6 to –1.6	12	–4.0	–11.6 to –2.6	12	–1.7	–4.7 to –1.2

[a] Negative favours supplements.
[b] Negative favours early tube feeding.
[c] Negative favours PEG tube feeding.
[d] None of the differences between job categories or countries were statistically significant.
[e] The four 'other' job categories were blank, dietitian, nurse and specialist nurse. The blank job category person did not give a response for Trial 3.
[f] The 'other' countries were Australia (2), Belgium (1), Canada (1), Denmark (1), Hong Kong (1), New Zealand (3), Portugal (2), Republic of Ireland (1).

might result in absolute differences of 10%, or even more, in our primary outcome. This reflects a tendency for clinicians to overestimate the likely effects of their treatments and contributes to the huge numbers of randomised trials which have been done that show a Type 2 error. Although we asked them to estimate the effects on our combined outcome – death or poor outcome – it is unclear whether their estimates would have differed substantially if we had asked them to estimate the effect on death alone. This may be important since in Trials 2 and 3 we saw a marked disparity, at least in our point estimates with respect to the different outcomes.

The clinicians' estimates of the direction and size of effect in Trial 1 suggested that almost all believed that the addition of oral supplements to normal hospital diet would improve patients' outcomes. A substantial minority believed that supplements would increase the absolute proportion with a good outcome by at least 3%; this size of effect is statistically very unlikely according to our results. Very few clinicians appeared to expect any likelihood of worse outcomes with supplements.

Their estimates with respect to the results of Trial 2 were generally in favour of early tube feeding, with more than 80% of clinicians expecting early feeding to improve outcomes. Although our estimate with respect to death or MRS 4–5 was only marginally in favour of early tube feeding, our estimate with respect to death alone was of a 5.8% (95% CI –0.8 to 12.5%) absolute reduction. This estimate would be very much in line with clinicians' expectations.

Most clinicians expected PEG feeding to improve patients' outcomes compared with NG feeding. This was opposite to the effect that we actually observed. Of course, our trial result with respect to death alone, where we saw only a small decrease with NG feeding, was more in keeping with at least a significant minority of clinicians.

These results, along with those from our feeding survey (Chapter 7), provide an indication of the practice and beliefs of UK stroke physicians.

Chapter 9
Main conclusions

In Trial 1, we have not shown a significant effect of routine oral nutritional supplements when they are given to a broad range of patients admitted to hospital with acute stroke. Our trial did not have sufficient power to exclude more modest differences overall (i.e. we could not reliably detect a 2–3% difference in the absolute proportion with a primary outcome) or even larger and clinically important effects in subgroups, such as those who were judged to be undernourished at baseline. Although we stopped recruitment before attaining our target of 6000 patients, it is statistically extremely unlikely that, had we reached this target, we would have confirmed the anticipated 4% absolute benefit from oral supplements used to estimate our sample size. It would require a sample size of perhaps 20,000–40,000 patients to detect reliably an advantage of 1–2% from supplements.

In Trial 2, we have not shown any statistically significant differences in outcomes between those allocated early and avoid enteral tube feeding. Nonetheless, there was an absolute difference in the risk of death in favour of early feeding of 5.8% (95% CI –0.8 to 12.5) and although this was not statistically significant at the 5% level, the 95% CIs were precise enough to make a clinically significant hazard from early tube feeding unlikely. There was also no excess of pneumonia associated with early tube feeding, which will reassure many clinicians.[60] However, the apparently better survival was offset by the 4.7% excess of survivors with a poor outcome, with worse QoL, among those allocated early tube feeding. Hence early feeding may keep patients alive but in a severely disabled state when they would otherwise have died. The Kaplan–Meier survival curves (*Figure 22*) diverge a couple of months after randomisation rather than in the early period. If there is a real difference in mortality between those tube fed early and late it would appear to have a delayed effect. Possibly earlier tube feeding leads to better nutritional status and patients' greater ability to resist potentially life-threatening complications such as infections.

In Trial 3, there was an absolute difference in the proportion of dead or poor outcome in favour of NG feeding of 7.8% (95% CI 0.0 to 15.5%; $p = 0.05$). The 95% CIs were precise enough to make a clinically significant benefit from PEG tube feeding, in preference to NG, highly unlikely.

Previous studies have indicated that PEG feeding is more effective at providing patients with adequate nutrition.[29–31] Our data on the practicality of tube feeding indicated that PEG tubes were rarely displaced and provided satisfactory feeding more often than NG. Hence, if our observation regarding the poorer functional outcomes in the PEG group is real, we have to look for an explanation which is not directly related to nutrition. Our expectation when conceiving the trial was that PEG might improve outcomes through delivering more effective nutritional support but that any benefits might be offset by the hazards of PEG insertion. In this trial, we have not demonstrated any major difference in mortality or the occurrence of complications which are likely to result from PEG insertion.

It is possible that the difference in MRS between the two groups is due to the effect that having a PEG *in situ* at final follow-up had on the assessment of the MRS. More patients allocated PEG (21%) were still receiving PEG feeding at final follow-up than those allocated NG (12%). It is possible that simply because the patient was being fed via a PEG, patients were judged more dependent. However, the survivors in the PEG arm were also more often, although not statistically significantly so, living in institutions and had a lower QoL.

The difference in feeding method at final follow-up might indicate that allocation to PEG feeding was associated with poorer recovery from dysphagia. However, an equally plausible explanation of the difference in feeding method is the failure of services to follow up PEG patients to establish if the tube can be safely removed. Several reports have highlighted how dysphagia after stroke may show recovery even months after stroke but that some patients are unnecessarily left with PEG tubes *in situ*.[34]

Another possible explanation for the observed difference for death or poor outcome is that

allocation to PEG, and presumably insertion of a PEG, was associated with a change in some other aspect of treatment which influences outcome. For instance, we wonder whether once a PEG has been inserted patients are considered to have been sorted out and they might therefore receive less input from nursing staff and other members of the multidisciplinary team. Certainly, patients with an NG *in situ* will usually have more regular attention from staff who might be reassessing swallowing ability to see if the tube can be removed and repositioning and checking the position of the NG tube. A patient with a PEG *in situ* will receive less of this type of attention. The excess of pressure sores in those in the PEG arm, if not just a chance finding or due to observer bias, might support this hypothesis, although it might also be due to patients' reluctance to move with a tube sticking out from their abdomen.

Worse outcomes in the PEG group might be explained in part by the greater delay to first tube feeding in the PEG arm (median 2 days, IQR 1–3) compared with the NG arm (median 0 days, IQR 0–1), but the results from Trial 2 suggest that this would be only a minor factor, assuming of course that the results of Trial 2 apply to the slightly different population enrolled in Trial 3.

Apparent excess of GI haemorrhage with tube feeding

One interesting finding in Trials 2 and 3 was the greater risk of GI haemorrhage in those who were tube fed and particularly those fed via an NG tube. Of course, in *Tables 22* and *32* we report the ITT analysis, which indicates the number of patients having bleeds according to their treatment allocation. When these cases were examined in more detail, it was apparent that the episodes of GI haemorrhage sometimes occurred after tube removal, or while an alternative tube was *in situ*. It may not be unreasonable to attribute a GI haemorrhage to a recently removed tube. We calculated the number of GI haemorrhages per 1000 patient days for each method of feeding. The rates were 2.8 per 1000 patient days for NG, 0.9 for PEG and 0.5 for neither. Of course, a problem with this analysis is that more GI haemorrhages occurred early when the patients were most sick and when they were most likely to be fed via an NG tube than any other. Where we had details of investigations of GI haemorrhage, the sources of bleeding varied but included gastritis, peptic ulcers and oesophageal, gastric and even pharyngeal tumours, generally reflecting the pathology reported in the literature.[61,62] Given that this was an unexpected finding, we had not systematically collected data to allow us to determine the cause of the GI haemorrhages. Some patients were judged too sick to undergo endoscopy. Any excess in NG-fed patients might plausibly result from direct trauma to the gastric mucosa or result from aspirin being put down the tube; however, in this trial we had insufficient data to explore the mechanism further. Of course, the strong trend towards reduced case fatality among those having early tube feeding takes account of any fatal GI haemorrhages.

Methodological issues

Failure to reach prespecified sample sizes

We did not achieve the targets set for enrolment. In Trial 1 we enrolled 67%, in Trial 2 43% and in Trial 3 just 32% of our recruitment targets, despite our best efforts. This inevitably limited the precision of our estimates of treatment effects and may have meant that we were unable to establish differences in outcomes where they exist.

Of course, the effect sizes on which power calculations are based are always a matter of judgement. Even pilot studies cannot provide a reliable indication, since if their estimates are precise it would negate the need for a larger trial. We chose effect sizes which we thought would be of clinical relevance and were plausible given our knowledge of stroke and the effects of other treatments. We did not think that the effect sizes found in the previous RCTs (*Figures 34* and *36*) were plausible, so we did not base our guesses on those. This judgement appears to have been confirmed as correct since our estimates are precise enough to make it highly unlikely that the effect sizes seen in previous trials are correct.[27,31]

Stopping recruitment prior to sample sizes being achieved can lead to bias in RCTs. For instance, if the decision to stop recruitment is based on the finding in an interim analysis of a statistically significant effect in either direction, then that result is likely to be an overestimate of the effect size. This is especially true if multiple interim analyses have been carried out. This is probably a greater problem in smaller trials performed in single centres and without independent data monitoring committees. Those recruiting into the trial and those deciding when to stop are often also managing the data. This may introduce systematic bias towards more extreme results in

small trials, which may in turn impact on the results of meta-analyses which summarise many small trials (e.g. *Figures 34* and *36*).

In the FOOD Trial, the steering committee decided to stop the trial before we had reached our target because there no funding to continue the trial beyond 2004 and they wished to ensure that the trial was closed out in an orderly manner. Our decision to stop was not based on knowledge of any interim analysis – indeed, the DMC had recommended continuation if at all possible. Hence it is unlikely that the decision to stop the trial before we had recruited our target numbers introduced bias into our estimates of treatment effect.

Although we did not achieve our prespecified sample sizes, these trials were far larger than any similar studies. Trial 1 was 10 times larger than any previous RCT of oral supplements in elderly patients (*Figure 34*) and was 100 times larger than the only previous RCT in hospitalised stroke patients.[27] Trial 2 is the first trial to assess the impact of early enteral tube feeding after stroke and Trial 3 is only the third trial comparing PEG and NG after stroke (*Figure 37*). It was 10 times larger than any previous trial comparing PEG and NG feeding in stroke patients.[31]

Effectiveness of randomisation procedures

Our central system of telephone randomisation where most baseline data were collected prior to treatment allocation proved very effective in achieving not only a very high level of completeness for baseline data but also an excellent balance for key prognostic factors and concealment of allocation.

Baseline assessment of swallowing ability

This was obviously an important issue for centres, since it determined which part of the FOOD Trial the patients were eligible to enter. Some might criticise us for not establishing a common, standardised method of swallow assessment with known validity and reliability across our centres. We considered that this was not necessary for the trial as it has no bearing on the assessment of treatment effect. We collected the method of screening on discharge during the latter half of the trial because we predicted that some might ask for these data. Most used a bedside assessment, usually including a water swallow test, and some were assessed by a speech and language therapist; very few had videofluoroscopy. The reliability of bedside swallowing assessments are generally moderate (Cohen's kappas of ~0.5), but one has to question how relevant reliabilities taken from single-centre studies are to a trial across so many centres in different countries.[20] There is no widespread agreement on a gold standard for assessing the validity of swallowing screens (videofluoroscopy is often used but does not meet all the criteria required of a 'gold standard').

Baseline assessment of nutritional status

Some might criticise our use of a simple and non-standardised assessment of baseline nutritional status which we used to stratify our patients. Even when fuller assessment was performed, there was no consistency. In some patients our global assessment was based on one individual measure and in others on a combination of measures.

However, our previous work summarised in Chapter 2 has shown our approach to have good concurrent and predictive validity and reasonable inter-rater reliability and to be practical in this sort of trial.[19,37] No alternative widely accepted global assessment of nutritional status was available when we established this trial.

Generalisability

The trial recruited from a wide range of hospitals in many countries, which increased its generalisability. We did not record the proportion of eligible patients enrolled in each centre by keeping logs of all stroke patients admitted to our centres during the trial, as to have attempted to do so would have greatly increased the resources required and diverted energies away from recruitment. Also, provided that one describes the patients enrolled, then describing those who were not enrolled adds relatively little to the generalisability of the results.

The relatively small proportion (7.8%) of patients enrolled into Trial 1 who were undernourished at baseline might indicate that many undernourished patients admitted to our hospitals were not enrolled but were given oral supplements outside the trial (owing to lack of clinician's 'uncertainty'). The small numbers of undernourished patients enrolled in Trial 1 certainly meant that we could only provide a very imprecise estimate of treatment effect in this subgroup.

Some might argue that any lack of treatment effects seen in these trials was due to our enrolling the wrong patients. Of course, a trial can only ever address the effectiveness of treatments in the

patients which it enrols. It is simply not ethical for a clinician to randomise a patient in a trial of alternative treatment if he/she believes that for that patient one of the treatments would be of greater benefit. If there was a clear indication for oral supplementation, early tube feeding or a particular type of tube, then it is to be hoped that patients were given that treatment. If there was a clear contraindication to tube feeding of a particular type, then it should have been withheld. Where the balance of risk and benefit was unclear, patients could be randomised. We explicitly used this uncertainty principle, which has been used in many other large, simple trials [e.g. International Stroke Trial (IST),[57] European Carotid Surgery Trial (ECST)[63]]. Even in trials which do not explicitly use this principle we would be surprised if patients for whom the responsible clinician was not substantially uncertain about the best treatment were enrolled. No RCT enrols all eligible patients and this always needs to be taken into account when applying the trial results to future patients.

The use of the uncertainty principle does not bias our estimate of the effects of treatment after randomisation. The targeting depended on the judgement of practising stroke physicians and therefore is likely to be appropriate given the purpose of the trial, namely to provide practising clinicians with information to guide their practice.

Completeness of data

This study had several methodological strengths. Follow-up was nearly 100% complete at 6 months and any loss to follow-up was of such a small order that it is unlikely to have led to significant bias.

Compliance and delivery of feeding regimes

Nutritional supplements may have been delivered to the patient but that does not guarantee consumption. Enteral tubes are sometimes difficult to place and retain and insertion of PEG tubes is often delayed because of limited services.[64,65] These problems are inherent to our interventions and are important to incorporate into any pragmatic assessment of the effectiveness of alternative feeding policies. We measured compliance and believe that it was satisfactory given the nature of the trial. We probably achieved better compliance than that achieved in normal clinical practice.

Measurement of precise nutritional intake in each treatment group

We did not record total nutritional intake (e.g. composition of normal hospital diet or exact composition of supplements and tube feeds). Although nutritionists might view this as a limitation, we established the FOOD Trial explicitly as a pragmatic trial to establish the impact of feeding policies on important clinical outcomes. The lack of detailed information regarding individual patients' nutritional intakes does not detract from the validity of this study. Detailed monitoring of the precise nutritional requirements of stroke patients and the extent to which these requirements are met is time consuming and is not deliverable in many stroke services, even within developed countries. Unfortunately, in an RCT which is large enough to provide information of relevant patient outcomes (e.g. survival, disability and QoL), it is not practicable to collect data of this detail without huge investment – investment which is simply not available for trials evaluating interventions with little commercial potential.

Hence our inability to demonstrate a large benefit from oral supplements may have been because either our policy and method of giving supplements did not result in the patient actually taking them or because normal hospital diets in our centres fully met the nutritional needs of the patients enrolled.

It is possible that the results of the tube feeding trials were influenced by the expertise of the staff in our centres in managing these regimes. It is likely that their expertise varied considerably across centres (as indeed it will do in everyday practice), but there is no indication that our centres were less expert than others. Indeed, one might expect centres which are willing to participate in a randomised trial and to expose themselves to external scrutiny to be more interested and perhaps better at these techniques. We were reassured by the low frequency of deaths attributed directly to tube insertion – frequencies which are comparable to those from the literature.[33–36] However, we acknowledge the major difficulties of attributing deaths to tube insertion (see below) unless the patients die from obvious peritonitis, tube-associated infection or haemorrhage.

Assessment of compliance with feeding regimes

Although compliance was not 100%, this reflects the inevitable difficulties of adhering to rigid schedules when patients' conditions change after randomisation, of clinicians, patients and families later expressing preferences for particular feeding regimes and the practical and logistic problems of instituting and continuing enteral tube feeding.

Lack of blinding of patients, carers and staff to treatment allocation

It would virtually be impossible to blind patients and hospital staff to the treatment allocation, but this means that there was the possibility that those allocated to avoid supplements could have been given extra food. However, very few patients in the no supplements groups actually received supplements. Also, we cannot exclude the possibility that other behavioural changes occurred secondary to the treatment allocation. Indeed, as already discussed, this seems the most likely explanation for the poorer functional outcomes seen in patients fed via a PEG tube in Trial 3.

Lack of blinding of assessment of adverse effects and complications

Our data concerning adverse effects of treatment and complication rates in hospital need to be interpreted with caution because of our lack of blinding to allocated treatment and the large number of statistical comparisons made, and it was not feasible to have local source data verified for the occurrence of complications. Indeed, it is also impossible to blind an assessor to the feeding regime if the assessment includes a review of casenotes unless one can delete all mention of treatment regimes from the records. This is particularly difficult if one is assessing adverse effects of the allocated treatment itself.

A small proportion of patients given supplements had these stopped prematurely because of hyperglycaemia. Hyperglycaemia has been associated with poor outcomes after stroke.[23] Hyperglycaemia could have offset some nutritional benefits of supplements and have partly explained our inability to identify a benefit from routine supplements. However, the proportions with hyperglycaemia were small and the effect of this is likely to have been negligible.

Were the primary outcomes appropriate?

Our main aim was to establish whether feeding policies influenced important clinical outcomes including survival and functional status. The MRS is an accepted standard, albeit imperfect, outcome scale which has been used in a large number of stroke trials. It therefore provides a common language for describing patients' outcomes. Our secondary outcomes included other important measures including complication and adverse event rates, LOS, residence and discharge and QoL.

Some might criticise our trial for not collecting information on nutritional outcomes (e.g. weight change during hospitalisation), but given the lack of evidence for effects on our primary outcomes (survival and MRS), in hospital complications, length of stay, residence at follow-up or QoL, one would have to question the relevance of any effect on such surrogate outcomes. We would argue that although nutritional status in survivors might help to explain some of the difference in clinical outcomes observed, it cannot do so satisfactorily since it would not be available in those who died. Also, measurement of nutritional status would not take account of other changes which may result from different feeding regimes (e.g. complications of tube feeding). In Trial 3, one would have expected better nutritional outcomes in those fed via a PEG tube – the data we have suggest that PEG much more often resulted in 'satisfactory feeding' and PEG tubes were far less often displaced than NG tubes. However, despite this, there was an apparent adverse effect of PEG on outcomes (which mainly affected functional status). We would need to know in much greater detail the nursing and therapy input for patients in each arm of the trial to explain this finding.

Blinding of primary outcome

Where the primary outcomes were assessed by telephone or face-to-face interview, the assessor was blinded to treatment allocation. Clearly, where patients, or their relatives, completed follow-up questionnaires they were not blinded to allocation, although it would be surprising if this introduced significant bias in the assessment of treatment effect.

Lack of source data verification

With the introduction of the European Clinical Trials Directive there is now greater emphasis placed on monitoring centres' compliance with the protocol and on-site source data verification. We did not perform either on-site monitoring or source data verification. However, we did carry out consistency checks and performed analyses to ensure that no centre produced data which were unusual. We also produced regular listings of missing or inconsistent data which were clarified with centres. One advantage of 'academic trials' in which there are no per patient payments to centres is that there is virtually no financial incentive to falsify data.

Implications for practice

The FOOD Trial addressed issues which arise in the management of stroke patients admitted to hospital in every country of the world. The trials

included a broad range of stroke patients including those who were able to swallow (Trial 1) or the remainder who have dysphagia (Trials 2 and 3). Unlike trials evaluating treatments which can only be applied to a minority of patients (e.g. thrombolysis), the FOOD Trial has very broad implications for clinical practice.

Oral supplements

According to our surveys, clinicians are currently likely to give supplements to those patients judged to be undernourished but not to those who appear normal or overweight. Prior to publication of the results of Trial 1, the clinicians believed that oral supplements were unlikely to be harmful and were likely to have small to moderate benefits. In Trial 1 we did not demonstrate any significant effect of routine oral nutritional supplements when they were given to stroke patients who by and large were well nourished on admission. Our trial did not have sufficient power to exclude modest differences in such patients, or even larger and clinically important effects in those who were undernourished. The updated meta-analysis (*Figures 34* and *35*) is consistent with a clinically significant effect on mortality in elderly medical patients overall and perhaps a more convincing one for those who are undernourished. Patients with stroke specifically were not shown definitely to benefit from supplements, but given that most stroke patients in the UK are currently managed by physicians coming from a geriatric medicine background, we believe those physicians are likely to apply the overall results of the systematic reviews to their stroke patients. Hence it seems likely that patients who are judged to be undernourished on admission, or who have deteriorating nutritional status during hospitalisation, will be offered oral nutritional supplements. Also, by placing more emphasis on nutrition after stroke we expect there to be more emphasis placed on nutritional assessment of stroke patients, both on admission and during their recovery.

Timing of enteral tube feeding

Since the FOOD Trial commenced, there has been a lot more emphasis on screening for and assessment of swallowing problems amongst hospital-admitted stroke patients. When the trial started it was not uncommon for dysphagic patients to be left without any feeding for a week or two. Our clinician survey in 2003 suggests that most clinicians would aim to feed patients via an NG within 1 week of admission. Of course, even if that is their aim, we do not know how often early feeding is achieved. Most clinicians believed that early tube feeding would improve outcomes.

Trial 2 did not demonstrate any statistically significant differences in outcomes between those allocated early and avoid enteral tube feeding. However, the risk of death was reduced in those fed early and, although this was not statistically significant, a clinically significant hazard from early tube feeding is very unlikely. However, early feeding may keep patients alive but in a severely disabled state when they would otherwise have died.

It seems likely, on these bases of current practice and these new data, that UK clinicians will generally adopt a policy of initiating enteral tube feeding amongst dysphagic stroke patients within the first 3–4 days of admission. In a significant minority of dysphagic stroke patients, difficult decisions have to be made about whether life-preserving treatment should be given, withheld or withdrawn.[66] These decisions should take into account the views of patients (where possible), their families and the clinical team. It is hoped that these decisions will be informed by our data indicating the likely impact of early tube feeding on mortality and functional outcome.

Method of early enteral tube feeding

Prior to the start of the FOOD Trial, many clinicians tried to avoid early tube feeding because of the practical difficulties they experienced in inserting and maintaining NG tubes. This had led to a trend towards earlier use of PEG tubes, which had been shown to provide more reliable feeding than NG tubes. Also, one well-publicised small trial had shown a large survival advantage with PEG tube feeding.[31] However, in most UK hospitals the limited access to early PEG tube feeding, which was a serious barrier to recruitment in the FOOD Trial, was also a reason why clinicians were unable to institute a policy of earlier use of PEG. Our clinician survey confirms that in 2003 UK clinicians would use PEG more often if their access to insertion was better and that clinicians believed that PEG tube feeding would improve patient outcomes.

The results of Trial 3 were unexpected. Trial 3 failed to confirm the large improvement in case fatality associated with PEG feeding. The systematic review of trials suggests that a major benefit on case fatality is unlikely (*Figure 36*). However, Trial 3 also suggested that functional outcome amongst survivors may be worse amongst those allocated PEG compared with those allocated NG. Even though this result was of borderline statistical significance, the 95% CIs were precise enough to make a clinically

significant benefit from PEG tube feeding highly unlikely.

Based on these data, we believe that Trial 3 is unlikely to alter substantially current clinical practice in the UK, where an NG tube is usually the first type of enteral tube used and PEG tubes are reserved for patients where NG tube feeding is either impractical or likely to be prolonged. However, the trial is likely to reduce the pressure on PEG services to expand to enable them to insert early PEGs. It may also be that until we have an explanation for the apparent adverse effects of PEG on functional outcome that clinicians will delay, and in some patients therefore avoid, PEG insertion.

The excess of pressure sores and the poorer functional outcomes among those allocated PEG might lead clinical teams to review the general care of these patients and for them to introduce more active mobilisation and to focus on ensuring that appropriate levels of rehabilitation continue. Our data on methods of feeding at final follow-up confirm that services should be available to review the need for continued PEG feeding once the patient has been discharged from acute or rehabilitation hospital.

Implications for future research

The FOOD Trial has shown that it is practical to perform large, multicentre international randomised trials of feeding interventions. Despite limited resources and streamlined trial procedures, we achieved excellent levels of data completeness.

Based on our survey of clinical practice and the likely interpretation that will be placed on our results, we think it is unlikely that further trials addressing our particular research questions will be performed in the foreseeable future. It is hoped that our trial will have emphasised once more that the results of small, single-centre trials such as those which preceded the FOOD Trial are an unreliable basis on which to develop clinical guidelines.

Oral supplements

Trial 1 indicated that any benefit from routine use of oral supplements in a generally well-nourished population of stroke patients is likely to be modest – of the order of a 0–3% absolute benefit. To demonstrate reliably such an effect size would require the randomisation of tens of thousands of patients. We do not think that there is the enthusiasm, sufficient clinical uncertainty amongst clinicians or the levels of research funding to allow such a trial to be performed. A trial focused on undernourished patients would be interesting but would be hampered by the lack of uncertainty and the unwillingness of clinicians not to give supplements to undernourished patients. It would probably be more acceptable to perform a trial of alternative regimes for supplementing the hospital diet, but such a trial would have to be very large to identify differences.

Tube feeding

Trial 2 indicated that earlier tube feeding may reduce case fatality and Trial 3 showed that PEG tube feeding in the first few weeks is unlikely to be associated with better outcomes. Hence one might expect clinicians to adopt a general policy of early tube feeding via NG tube. However, there are still major concerns regarding the efficient and safe delivery of NG feeding. There has been little formal research into how NG feeding can be optimised in stroke patients.

Important research questions regarding NG feeding include:

1. What methods of tube insertion are most likely to lead to correct placement of the NG tube? Our impression is that few medical or nursing staff receive any formal training in tube insertion. Hence one might ask whether proper training improves the success rates. Also, are techniques such as induction of a swallow reflex[55] or radiographic guidance, which have been suggested, safe and cost-effective?
2. What is the most practical and effective method, or combination of methods, to ensure that the tube is actually in the stomach? Injection of air and auscultation over the stomach, aspiration of gastric contents and measurement of their pH and X-ray examination are widely but variably used to confirm proper placement. However, the research basis underlying these techniques is inadequate.
3. Probably the most common problem encountered with NG feeding in stroke patients is displacement of the tube. This may lead to interruption of hydration, feeding and medication, with important consequences for the patient. Various methods of physical restraint are used to increase the likelihood of retention of tubes. These include the use of mittens, nasal loops,[65,67] sutures, tying patients hands to cot sides and even an American football helmet. In the UK there is an

understandable reluctance to use restraints of this type, but their use varies considerably across hospitals in the UK and to an even greater extent between countries. There are no reliable studies to establish the balance of risk versus benefits of these techniques or to establish patients' and carers' attitudes towards them. Such studies are required to guide clinical practice.

4. Our observation that GI haemorrhage appears to be more common amongst those stroke patients who are tube fed and especially amongst those fed via an NG tube appears to be new. Indeed, in critical care early tube feeding is often employed in the belief that it will actually decrease the risk of GI haemorrhage. Further studies are needed to confirm our finding and to establish the reasons why there may be an excess of haemorrhage. This might then lead on to further work to establish whether the risks can be reduced – perhaps by using rectal aspirin instead of putting it down an NG tube or by routine use of acid-suppressing medications.[68,69]

Our observation that although PEG feeding may not be associated with higher mortality it may be associated with worse outcomes warrants further study. Observational research might establish whether the general approach to caring for stroke patients is altered by having a PEG *in situ* and that this might lead to worse functional outcomes. This work is important since although PEG tubes may be used less often in the first few weeks after stroke, they will still be required in those patients in whom NG feeding cannot be maintained or where longer term tube feeding is necessary. We need to optimise the outcomes in these patients.

Some of this research is already in progress and it is hoped that this sort of research will be facilitated by the development of the Stroke Research networks throughout the UK. We hope we can look forward to a future where our policies for feeding stroke patients are based on more reliable evidence and there is less variation in feeding policies for stroke patients, so that all patients receive the most effective regime.

Acknowledgements

FOOD was funded by the NHS R&D Health Technology Assessment Programme (Reference 96/29/01), The Stroke Association (Reference 17/98) and Chest Heart and Stroke Scotland (Reference 97/4). The Singapore Medical Research Council supported the trial in Singapore. The Royal Australasian College of Physicians supported the trial in Hawkes Bay, New Zealand.

We gratefully acknowledge the help of the following people:

- The trial participants, without whom the trial could not have happened
- Members of the Independent Data Monitoring Committee: Professor CJ Bulpitt, Professor A Grant (Chair), Professor G Murray and Professor P Sandercock.
- Members of the Steering Committee: Mrs G Bathgate, Mr C Chalmers, Ms G Cranswick, Professor MS Dennis, Ms B Farrell, Professor J Forbes (Grantholder), Professor S Ghosh, Professor P Langhorne, Dr S Lewis, Mrs J MacIntyre, Ms CA McAteer, Dr P O'Neill, Dr J Potter, Dr M Roberts and Professor C Warlow.
- The National Coordinators: Dr N Anderson (New Zealand), Dr S Bahar (Turkey), Professor G Hankey (Australia) and Dr S Ricci (Italy).
- The Cochrane Group Collaborators (who provided updated systematic review of oral supplements): Dr J Potter, A Milne, A Avenell. Also Professor D Barer, Gateshead, who provided data from the PEGASUS trial for us to include in our updated systematic review.
- The staff at the Co-ordinating Centre in Edinburgh: Ms J Clarke (Secretary), Ms G Cranswick (Trial Coordinator), Professor MS Dennis (Principal Investigator and Grantholder), Mrs R Flaig (Interim Trial Co-ordinator), Mrs A Fraser (Data Management Team), Mrs S Grant (Data Management Team), Mrs A Gunkel (Interim Trial Coordinator), Ms J Hunter (Data Management Team), Dr S Lewis (Trial Statistician), Mr D Perry (IT Manager), Mrs V Soosay (Computer Programmer), Mrs Carol Williams (Recruitment Coordinator), Mrs A Williamson (Trial Secretary) and Mr A Young (Data Management Team).
- The Collaboration. Only those centres who recruited one or more patients have been acknowledged. The numbers in parentheses are the total numbers of patients randomised by the centre.

001, Western General Hospitals NHS Trust, Edinburgh, UK (282), Professor MS Dennis, Dr R Lindley, Ms D Shaw, Ms P Taylor

002, Ulster Hospital, Belfast, UK (148), Dr J Finnerty, Dr MJP Power

003, Stirling Royal Infirmary, Stirling, UK (23), Mrs FJ Dick, Dr D Kennie

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005, Nottingham City Hospital, Nottingham, UK (4), Professor P Bath, Dr P Berman, Mr C Weaver

006, Hereford General Hospital, Hereford, UK (22), Dr PW Overstall, Ms M Probert, Dr E Wales

007, Bronllys Hospital, Brecon, UK (10), Dr J Buchan, Dr A Dunn, Sister J Hallam, Dr S Manthri, Mrs J Williams

008, Christchurch Hospital NHS Trust, Christchurch, UK (156), Ms A Graham, Dr A Hanrahan, Dr D Jenkinson, Dr J Kwan, Dr S Ragab

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041, Northwick Park Hospital, Harrow, UK (150), Mrs K Butchard, Dr DL Cohen

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053, St John's Medical College Hospital, Bangalore, INDIA (573), Mr Ananadan, Dr U Devraj, Dr JM Jose, Dr T Manjari, Dr L Pinheiro, Professor AK Roy

055, Singapore General Hospital, Singapore (78), Miss CF Chan, Dr H-M Chang, Dr CPL-H Chen, Mr HPA Goh, Dr W Luman, Dr MC Wong

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081, Ruttonjee Hospital, Wanchai, Hong Kong (21), Dr KY Chan, Dr ESL Chow, Dr CKL Kng, Dr CP Wong

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089, Barnsley District General Hospital, Barnsley, UK (79), Dr MK Al-Bazzaz, Mrs BM Hardware, Mr JD Hitchcock, Dr AI Khan

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Appendix 1
Dissemination

Presentations at meetings

Those in italics were presented by grantholder personally. Others were presented by collaborators.

Country	Meeting	Date
UK	Steering Committee, Edinburgh	04/05/2004
Germany	*Collaborators Meeting, Mannheim*	*12/05/2004*
Germany	*European Stroke Conference, Mannheim*	*15/05/2004*
UK	Fazakerely Hospital, Liverpool	20/05/2004
Republic of Ireland	*Irish Heart Foundation Stroke Meeting, Dublin*	*21/05/2004*
UK	*Stroke Research Group, Edinburgh*	*26/05/2004*
Republic of Ireland	St Vincent's Hospital, Dublin	27/05/2004
Australia	Westmead Hospital, Sydney	02/06/2007
UK	Belfast City Hospital	07/06/2004
UK	*Scottish Stroke Collaboration, Edinburgh*	*14/06/2004*
Canada	*World Stroke Congress, Vancouver*	*25/06/2004*
Australia	Alexandra Hospital, Brisbane	28/06/2004
New Zealand	Hawkes Bay Hospital	01/07/2004
Republic of Ireland	St James's Hospital, Dublin	01/08/2004
Australia	Westmead Hospital, Sydney	25/08/2004
UK	St Mary's Hospital, London	26/08/2004
UK	*Leeds Nutrition Course*	*08/09/2004*
UK	Charing Cross Hospital, London	09/09/2004
UK	*Stroke Association Conference, Cambridge*	*15/09/2004*
UK	University of Ulster	24/09/2004
UK	*Western General Hospital*	*29/09/2004*
Austria	4th Austrian Stroke Unit Meeting	04/10/2004
Turkey	Turkish National Neurology Congress	29/09/2004
Belgium	Postacademic Course on Dysphagia, Bruges	10/2004
UK	*British Geriatric Society*	*06/10/2004*
Australia	Stroke Society of Australasia Annual Scientific Meeting, Hobart	13/10/2004
Russia	VIII International Congress of Parenteral and Enteral Nutrition, Moscow	13/10/2004
UK	West Cumberland Hospital	26/10/2004
UK	Borders General Hospital	27/10/2004
UK	Gloucestershire Royal Hospital	23/11/2004
UK	Birmingham Heartland Hospital	25/11/2004
UK	*Welsh Stroke Conference, Gwent*	*26/11/2004*
UK	Huddersfield Royal Infirmary	?/11/2004
Italy	Italian Neurological Society Meeting, Genova	09/2004

Publications in peer-reviewed journals

The FOOD Trial Collaboration. Performance of a statistical model to predict stroke outcome in the context of a large simple randomised controlled trial of feeding. *Stroke* 2003;**34**:127–33.

The FOOD Trial Collaboration. Poor nutritional status on admission predicts poor outcomes after stroke: observational data from the FOOD trial. *Stroke* 2003;**34**:140–56.

The FOOD Trial Collaboration. Routine oral nutritional supplementation for stroke patients in hospital (FOOD): a multicentre randomised controlled trial. *Lancet* 2005;**365**:755–63.

The FOOD Trial Collaboration. Effect of timing and method of enteral tube feeding for dysphagic stroke patients (FOOD): a multicentre randomised controlled trial. *Lancet* 2005; **365**:764–72.

National guidelines (e.g. SIGN)

The preliminary results have been referred to in the SIGN guidelines on dysphagia after stroke:

Scottish Intercollegiate Guidelines Network (SIGN). *Management of patients with stroke 111: identification and management of dysphagia*. Edinburgh: SIGN Secretariat; 2004.

Those responsible for the Swedish national stroke guidelines have requested and received the results of the trial.

The Cochrane Collaboration

The data from Trial 1 have been incorporated into the following:

Milne AC, Potter J, Avenell A. Protein and energy supplementation in elderly people at risk from malnutrition (Cochrane Review). *The Cochrane Library* Issue 2. Chichester: John Wiley; 2004.

Those from Trials 2 and 3 are being incorporated into an updated version of the following:

Bath PMW, Bath FJ, Smithard DG. Interventions for dysphagia in acute stroke (Cochrane Review). *The Cochrane Library*, Issue 1. Oxford: Update Software; 2002.

The FOOD website (www.dcn.ed.ac.uk/food)

We have posted the results of the trial on our website.

Appendix 2

Randomisation form

The International Stroke Trials Collaboration
(Feed Or Ordinary Diet)

RANDOMISATION FORM

Do NOT randomise unless you are uncertain about the best feeding policy for your patient

PLEASE BE READY TO PROVIDE THE FOLLOWING INFORMATION WHEN YOU MAKE THE RANDOMISATION TELEPHONE CALL ON ☐☐☐☐☐☐☐☐☐☐

Has this patient been randomised into the FOOD trial before? No ☐ **(KEY 0)** Yes ☐ **(KEY 1)**

HOSPITAL DETAILS:

Country: ☐☐☐☐☐☐☐☐☐☐ Country number: ☐☐☐

Hospital Name: ☐☐☐☐☐☐☐☐☐☐ Hospital number: ☐☐☐

Name of responsible Consultant: ☐☐☐☐☐☐☐☐☐☐ Consultant number: ☐☐☐☐

Randomising doctor: ☐☐☐☐☐☐☐☐☐☐

Consent: Has consent been given? Yes ☐ (**MUST** be Yes) **(KEY 1)**

PATIENT DETAILS:

Family Name: ☐☐☐☐☐☐☐☐☐☐ Given Name/s: ☐☐☐☐☐☐☐☐☐☐

Date of Birth: ☐☐/☐☐/☐☐☐☐ (day/month/year) Sex? Male ☐ **(KEY 1)** Female ☐ **(KEY 2)**

Date stroke symptoms first noticed: ☐☐/☐☐/☐☐☐☐ (day/month/year) Date of admission: ☐☐/☐☐/☐☐☐☐ (day/month/year)

ABOUT THE PATIENT: *(the following questions will be asked by number)*

		(KEY 1) Yes	(KEY 0) No	(KEY 9) Don't Know
1	Did the patient live alone before admission?	☐	☐	☐
2	Was the patient independent in every day activities before this stroke?	☐	☐	☐

ABOUT THE STROKE: *(the following questions will be asked by number)*

Is the patient:

		(KEY 1) Yes	(KEY 0) No
3	able to talk **and** orientated in time, place and person?	☐	☐
4	able to lift **both** their arms off the bed?	☐	☐
5	able to walk without help from another person?	☐	☐
6	able to swallow liquids safely?	☐	☐

7 Do you think the patient is: *(Tick **one** box only)* Under-nourished? ☐ **(KEY 1)** Normal? ☐ **(KEY 2)** Overweight? ☐ **(KEY 3)**

8 **Can the patient take adequate fluids orally?**
- Yes ☐ (For **Yes — Key 1**) (For **No — Key 0**)
- No ☐

TRIAL 1 — tick
- **Randomise between Normal diet until discharge** ☐
- **vs**
- **Normal diet PLUS oral supplements** (prescribe 120ml 3x per day) ☐

9 **Within 1st week of admission are you uncertain whether to tube feed NOW or DELAY for at least a week?**
- Yes ☐
- No ☐

TRIAL 2 — tick
- **Randomise between Immediate tube feeding** ☐
- **vs**
- **Delay tube feeding for at least a week** (and hydrate using parenteral fluids) ☐

10 **If you are going to start tube feeding NOW are you uncertain whether to use an NG or PEG tube?**
- Yes ☐
- No ☐

TRIAL 3 — tick
- **Randomise between Nasogastric tube feeding** ☐
- **vs**
- **PEG tube feeding** ☐

11 **If you are certain, which type of tube will you use?**
- NG ☐ **(Key 3)**
- PEG ☐ **(Key 4)**

Thank You — Now please post or fax this form if you have used the automated randomisation service. Please keep the original for your records

Fax: +44(0) 131 332 5150

FOOD/SE/1/998

Randomisation form: reverse

NOTES

Using the automated service

Please note that you will not be able to make a reverse charge call to this service.

Remember to fax us the Randomisation Form every time the automated service is used. Our fax number is +44 (0) 131 332 5150.

If you would like to practise using this service, please call the number provided on the front of the FOOD manual.

If you experience any difficulties with this service please fax us the completed Randomisation Form and we will return it to you with the treatment allocation clearly marked.

About the Stroke

- These questions relate to the Glasgow Coma Scale (GCS) or the Medical Research Council (MRC) Scale
- Able to swallow - *This assessment should be performed in line with local guidelines but, as a minimum, should comprise a bedside assessment*
- Nourishment - *This assessment should be performed in line with local practice but, as a minimum, should include an informal assessment of nutritional status*

Co-enrolment

Remember you can randomise this patient into another trial if you are uncertain how best to feed them later in this admission (e.g. NG vs PEG, Normal diet vs Normal diet PLUS oral supplements).

FOOD/SER/1/998

Appendix 3

Adverse event card

Please complete if any patient randomised into FOOD experiences a **major adverse event** (in particular any relating to the allocated feeding policy)

TO MAINTAIN CONFIDENTIALITY, PLEASE SEND US THIS CARD IN AN ENVELOPE

Hospital name: _____

Patient's family name: _____

Given names: _____

Date of birth: day_____/month_____/year_____

Date adverse event first experienced: day_____/month_____/year_____

Details: _____

_____

_____ ☐☐

for office use only

Please return (in an envelope) to the FOOD Trial Co-ordinating Centre, Neurosciences Trials Unit, Western General Hospital, Edinburgh, EH4 2XU

THANK YOU

for office use only ☐☐☐ ☐☐☐☐☐

FOOD/MAC/1/998

Appendix 4

Hospital discharge form

Page 1

The International Stroke Trials Collaboration (Feed Or Ordinary Diet)

Hospital Discharge Form

PLEASE COMPLETE THIS FORM ON THE PATIENT'S DISCHARGE FROM HOSPITAL, TRANSFER FROM THE CENTRE OR DEATH (whichever occurs first) AS ACCURATELY AS POSSIBLE

Hospital Details:

Hospital Number: ☐☐☐ or Hospital Name: _____

Patient Details:

Family Name: _____

Given Name/s: _____

Date of Birth: day ☐☐ month ☐☐ year ☐☐☐☐

Sex: Male ☐ Female ☐

Affix Patient Sticker Here

ABOUT THE STROKE:

Was stroke diagnosis confirmed in this patient? YES ☐ NO ☐

If **not** a stroke, please specify the diagnosis: _____ ☐☐

For office use

ABOUT THE PATIENT:

How was the nutritional status assessed before first randomisation *(please tick (✓) one or more boxes)*

- ☐ Informal assessment
- ☐ Weight
- ☐ Dietitian's assessment
- ☐ Anthropometry
- ☐ Blood tests
- ☐ Other: _____ ☐☐

For office use

How was the swallowing assessed before the first randomisation *(please tick (✓) one or more boxes)*

- ☐ Bedside assessment (doctor or nurse)
- ☐ Bedside assessment (speech & language therapist)
- ☐ Videofluoroscopy
- ☐ Other: _____ ☐☐

For office use

PRIOR to randomisation, did this patient receive:

Any enteral tube feeds? YES ☐ NO ☐

SINCE randomisation, has this patient received*: (please tick (✓)* ***one*** *box on* ***each*** *line)*

Any Parenteral Fluids	YES ☐	NO ☐	If **YES** complete PARTS 1, 5, 6 & 7
Any feeding via an NG Tube	YES ☐	NO ☐	If **YES** complete PARTS 2, 5, 6 & 7
Any feeding via another type of tube (e.g. PEG)	YES ☐	NO ☐	If **YES** complete PARTS 3, 5, 6 & 7
Any normal hospital diet PLUS supplementary feed	YES ☐	NO ☐	If **YES** complete PARTS 4, 5, 6 & 7
Normal hospital diet only	YES ☐	NO ☐	If **YES** complete PARTS 5, 6 & 7

Other (e.g. total parenteral nutrition), *please specify*: _____ ☐☐

For office use

If allocated feeding policy(ies) was(were) **not** followed please give reason(s) below:

_____

_____ ☐☐

For office use

FOOD/D/2/998/ *page 1*

Page 2

PART 1 Parenteral Fluids Given SINCE Randomisation (Please enter 99/99/99 or 99 if unknown)

Route: *(please tick (✓) one box)* ☐ Intravenous ☐ Subcutaneous ☐ Both

Date first parenteral fluids given after randomisation: day ☐☐ month ☐☐ year ☐☐☐☐

Date last parenteral fluids given: day ☐☐ month ☐☐ year ☐☐☐☐

Were fluids given between these dates? ☐ Continuously ☐ Intermittently

PART 2 Fed via a NG Tube SINCE Randomisation (Please enter 99/99/99 or 99 if unknown)

Date first NG tube inserted after randomisation: day ☐☐ month ☐☐ year ☐☐☐☐

Number of tubes inserted SINCE randomisation: ☐

Is the NG tube still in situ? YES ☐ NO ☐

If **NO**, date last NG tube removed: day ☐☐ month ☐☐ year ☐☐☐☐

Name(s) of feed given: _____

Did NG tube deliver satisfactory volumes of liquid feed? YES ☐ NO ☐ Uncertain ☐

If NG feeding stopped, please indicate the primary reason below *(please tick (✓) **one** box **only**)*

☐ Patient taking adequate diet and fluids orally
☐ Patient discharged/died
☐ Difficulties encountered ***(please specify difficulties below)***
☐ Other (e.g. feeding futile), *please specify:* _____ ☐☐ For office use

Were any difficulties experienced? *(please tick (✓) **one** or **more** boxes)*

☐ **No**
☐ Difficulties with tube insertion ☐ Patient pulled out the tube(s)
☐ Nasal ulceration ☐ Aspiration
☐ Other, *please specify:* _____ ☐☐ For office use

PART 3 Fed via another type of tube (e.g. PEG) SINCE Randomisation (Please enter 99/99/99 or 99 if unknown)

Type of tube inserted ☐ Gastric ☐ Duodenal/jejunal

Method of insertion ☐ Endoscopic ☐ Radiological guidance

Date first tube inserted after randomisation: day ☐☐ month ☐☐ year ☐☐☐☐

Number of tubes inserted SINCE randomisation: ☐

Is the tube still in situ? YES ☐ NO ☐

If **NO**, date last tube removed: day ☐☐ month ☐☐ year ☐☐☐☐

Name(s) of feed given: _____

Did PEG tube deliver satisfactory volumes of liquid feed? YES ☐ NO ☐ Uncertain ☐

If PEG feeding stopped, please indicate the primary reason below *(please tick (✓) **one** box **only**)*

☐ Patient taking adequate diet and fluids orally
☐ Patient discharged/died
☐ Difficulties encountered ***(please specify difficulties below)***
☐ Other (e.g. feeding futile), *please specify:* _____ ☐☐ For office use

Were any difficulties experienced? *(please tick (✓) **one** or **more** boxes)*

☐ **No**
☐ Difficulties with tube insertion ☐ Patient pulled out the tube(s)
☐ Wound infection ☐ Aspiration
☐ Haemorrhage from PEG site ☐ Peritonitis
☐ Other, *please specify:* _____ ☐☐ For office use

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Page 3

PART 4 Supplementary Feeds Given SINCE Randomisation (Please enter 99/99/99 or 99 if unknown)

Date supplementary feeding started since randomisation: day ☐☐ month ☐☐ year ☐☐☐☐

Number of **missed** doses SINCE randomisation: ☐☐ (Should receive 3 doses per day)

Are supplementary feeds still being given ? YES ☐ NO ☐

If **No**, date last supplementary feed given: day ☐☐ month ☐☐ year ☐☐☐☐

Name(s) of feed given: _____

If supplementary feeding stopped, please indicate the primary reason below *(please tick (✓) **one** box **only**)*

☐ Patient discharged/died

☐ Difficulties encountered ***(please specify difficulties below)***

☐ Other (e.g. feeding no longer appropriate), *please specify:* _____ ☐☐ For office use

Were any difficulties experienced? *(please tick (✓) **one** or **more** boxes)*

☐ **No**

☐ Unable to swallow ☐ Patient refused ☐ Unwanted weight gain

☐ Any other, *please specify:* _____ ☐☐ For office use

PART 5 This section should be completed for all patients (Please enter 99/99/99 or 99 if unknown)

SINCE this patient was first randomised have they experienced any of the following: No ☐

☐ Recurrent stroke — If so, first noted **since** randomisation day ☐☐ month ☐☐ year ☐☐☐☐

☐ Neurological worsening (not clearly due to recurrence) — If so, first noted **since** randomisation day ☐☐ month ☐☐ year ☐☐☐☐

☐ Pneumonia — If so, first noted **since** randomisation day ☐☐ month ☐☐ year ☐☐☐☐

☐ Other infections 1 — If so, first noted **since** randomisation day ☐☐ month ☐☐ year ☐☐☐☐

Please specify: _____ ☐☐ For office use

2 If so, first noted **since** randomisation day ☐☐ month ☐☐ year ☐☐☐☐

Please specify: _____ ☐☐ For office use

☐ Pulmonary embolism — If so, first noted **since** randomisation day ☐☐ month ☐☐ year ☐☐☐☐

☐ Deep vein thrombosis — If so, first noted **since** randomisation day ☐☐ month ☐☐ year ☐☐☐☐

☐ Pressure sores — If so, first noted **since** randomisation day ☐☐ month ☐☐ year ☐☐☐☐

☐ Gastrointestinal haemorrhage — If so, first noted **since** randomisation day ☐☐ month ☐☐ year ☐☐☐☐

☐ Other medical complications 1 — If so, first noted **since** randomisation day ☐☐ month ☐☐ year ☐☐☐☐

Please specify: _____ ☐☐ For office use

2 If so, first noted **since** randomisation day ☐☐ month ☐☐ year ☐☐☐☐

Please specify: _____ ☐☐ For office use

Did the patient survive to discharge from randomising centre?

YES ☐ NO ☐ If **YES**, go to Part 6

If **NO**, please complete the following

Date of death day ☐☐ month ☐☐ year ☐☐☐☐

Primary cause of death *(please tick (✓) **one** box **only**)*

☐ Neurological damage from initial stroke (e.g. coning) ☐ Pneumonia ☐ Pulmonary embolism

☐ Recurrent stroke ☐ Coronary heart disease

☐ Other vascular, *please specify:* _____ ☐☐

☐ Non-vascular, *please specify:* _____ ☐☐ For office use

Do you think this patient died due to trial treatment? YES ☐ NO ☐

If **YES**, *please specify:* _____ ☐☐ For office use

Cause of death confirmed by autopsy? YES ☐ NO ☐

Page 4

PART 6 FOLLOW-UP DETAILS

Has this patient been discharged to: *(tick (✓) **one** box **only**)*

☐ own home, alone ☐ at home, with partner or relative ☐ relative's home
☐ residential home ☐ nursing home ☐ other hospital
☐ other, *please specify:* _____ ☐☐

For office use

If so, **date of discharge** day ☐☐ month ☐☐ year ☐☐☐☐

Patient details:

Patient's full postal address on discharge
(please **PRINT** clearly or attach an address label)

Post Code **Telephone:**

Family doctor details:

Name of family doctor on discharge

Family doctor's full postal address
(please **PRINT** clearly)

Post Code **Telephone:**

If this patient is NOT registered with a family doctor, please provide the name of a reliable contact below:

Contact Name

Relationship to patient

Full postal address
(please **PRINT** clearly)

Post Code **Telephone:**

Part 7 Additional Information

(Please use this space below for any additional information you may think relevant to the trial or to the patient's treatment)

_____

_____

_____

_____

_____

_____

_____ ☐☐

For office use

Form completed by:

Date:

Thank you

Now please photocopy this form (for your own records) **and send the ORIGINAL to the FOOD Trial Co-ordinating Centre, Neurosciences Trials Unit, Western General Hospital, Edinburgh EH4 2XU SCOTLAND using the envelopes provided or Fax on +44 (0) 131 332 5150**

FOOD/D/2/998/ *page 4*

Appendix 5

Follow-up form

The International Stroke Trials Collaboration (Feed Or Ordinary Diet)

FOLLOW-UP QUESTIONNAIRE

CONFIDENTIAL

Dear

On:

you were admitted to:

under the care of:

and, we would like to know how you are now. We need to know what you are **actually managing** to do now, not what you used to do, or would like to do.

Please tick (✓) one box on each line

	YES	NO
Has the stroke left you with any problems?	☐	☐
Do you need help **from anybody** with everyday activities?	☐	☐

How do you live now? *(please tick (✓) **ONE** box only)*

On my own	☐	☐
With my partner or relatives	☐	☐

Where do you live now? (*please tick* (✓) ***ONE*** *box only*)

In my own home or my relative's home	☐	☐
In a residential home	☐	☐
In a nursing home	☐	☐

In the next section we would like you to read the following descriptions from people who have had similar medical problems to you and choose the one which best describes your present state.

Tick the ONE box next to the sentence which best describes your present state.

- ☐ I have no symptoms at all
- ☐ I have a few symptoms but these do not interfere with my everyday life
- ☐ I have symptoms which have caused some changes in my life but I am still able to look after myself
- ☐ I have symptoms which have significantly changed my life and I need some help in looking after myself
- ☐ I have quite severe symptoms which mean I need to have help from other people but I am not so bad as to need attention day and night
- ☐ I have major symptoms which severely handicap me and I need constant attention day and night

We would also like to know how you are NOW being fed

- ☐ I now consider that I can eat normally
- ☐ I am fed via a tube in my nose
- ☐ I am fed via a tube in my side

NOW PLEASE TURN OVER

FOOD/FU/1/898

Reverse

HEALTH SURVEY

By placing a tick (✓) in ONE box in EACH group below, please indicate which statements best describe your own health state today.

Mobility
- I have no problems in walking about ☐
- I have some problems in walking about ☐
- I am confined to bed ☐

Self-Care
- I have no problems with self care ☐
- I have some problems with washing or dressing myself ☐
- I am unable to wash or dress myself ☐

Usual Activities
- I have no problems with performing my usual activities (eg work, study, housework, family or leisure activities) ☐
- I have some problems performing my usual activities ☐
- I am unable to perform my usual activities ☐

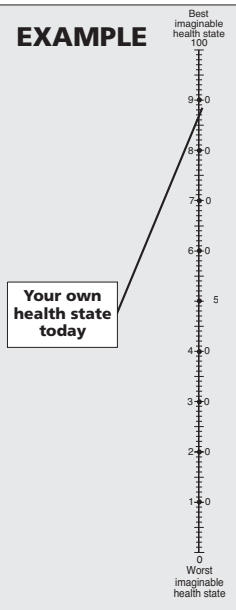
Pain/discomfort
- I have no pain or discomfort ☐
- I have moderate pain or discomfort ☐
- I have extreme pain or discomfort ☐

Anxiety/depression
- I am not anxious or depressed ☐
- I am moderately anxious or depressed ☐
- I am extremely anxious or depressed ☐

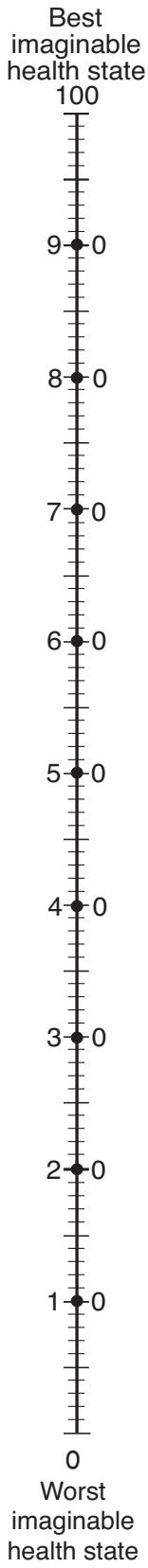
To help people say how good or bad a health state is, we have drawn a scale (rather like a thermometer) on which the best state you can imagine is marked by '100' and the worst state you can imagine is marked by '0'

Following the example on the right we would like you to indicate on this scale how good or bad your health is today, in your opinion.
Please do this by drawing a line from the box **'Your own health today'** to whichever point on the scale indicates how good or bad your current state is.

EXAMPLE



Your own health state today



Did you complete this form yourself (please tick (✓) one box)? Yes ☐

No, it was completed by a relative or friend ☐

Today's date: ☐☐ day ☐☐ month ☐☐☐☐ year

Thank you very much for taking the time to complete this form. Please return it using the pre-paid envelope provided

FOOD/FU/1/898

Appendix 6

Follow-up: hospital version

The International Stroke Trials Collaboration
(Feed Or Ordinary Diet)

Doctors questionnaire – patient still in hospital at 6 months

FOLLOW-UP QUESTIONNAIRE

CONFIDENTIAL

Dear

Re:

On:

the above named patient was admitted to:

under your care. It is now time for the six month follow-up of _____ and we understand that this patient is still in hospital. We need to know what _____ can **actually manage** to do now.

Please tick (✓) ONE box on each line

	YES	NO
Has the stroke left your patient with any problems?	☐	☐
Does your patient need help **from anybody** with everyday activities?	☐	☐

Does your patient *(please tick (✓) **ONE** box only)*

	YES	NO
Have an NG tube in situ	☐	☐
Have a PEG tube in situ	☐	☐

Where is the patient NOW?

Hospital: ☐

Ward: ☐

Who is responsible for their daily care (if this is NOT you)

☐

Please complete this form by asking the following questions.
In the next section we would like your patient to read the following descriptions and choose the one which best describes their present state. If your patient cannot read or complete the questionnaire, please complete it on their behalf.

Tick the ONE box next to the sentence which best describes your present state.

- ☐ I have no symptoms at all
- ☐ I have a few symptoms but these do not interfere with my everyday life
- ☐ I have symptoms which have caused some changes in my life but I am still able to look after myself
- ☐ I have symptoms which have significantly changed my life and I need some help in looking after myself
- ☐ I have quite severe symptoms which mean I need to have help from other people but I am not so bad as to need attention day and night
- ☐ I have major symptoms which severely handicap me and I need constant attention day and night

NOW PLEASE TURN OVER

FOOD/FU6/1/898

Reverse

HEALTH SURVEY

By placing a tick (✓) in ONE box in EACH group below, please indicate which statements best describe your own health state today.

Mobility
- I have no problems in walking about ☐
- I have some problems in walking about ☐
- I am confined to bed ☐

Self-Care
- I have no problems with self care ☐
- I have some problems with washing or dressing myself ☐
- I am unable to wash or dress myself ☐

Usual Activities
- I have no problems with performing my usual activities (eg work, study, housework, family or leisure activities) ☐
- I have some problems performing my usual activities ☐
- I am unable to perform my usual activities ☐

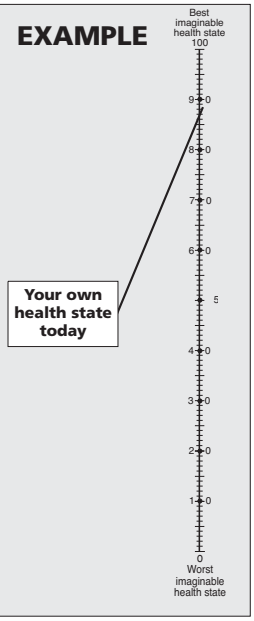
Pain/discomfort
- I have no pain or discomfort ☐
- I have moderate pain or discomfort ☐
- I have extreme pain or discomfort ☐

Anxiety/depression
- I am not anxious or depressed ☐
- I am moderately anxious or depressed ☐
- I am extremely anxious or depressed ☐

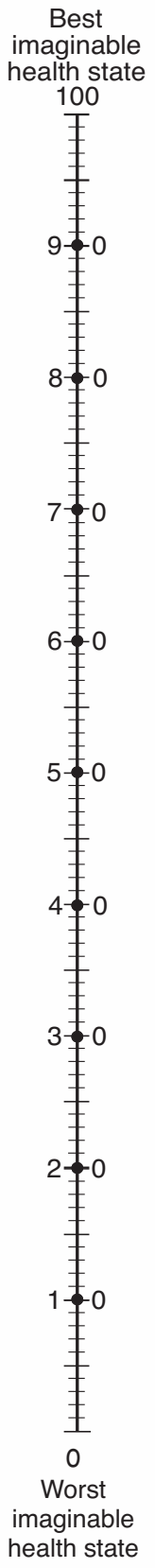
To help people say how good or bad a health state is, we have drawn a scale (rather like a thermometer) on which the best state you can imagine is marked by '100' and the worst state you can imagine is marked by '0'

Following the example on the right we would like you to indicate on this scale how good or bad your health is today, in your opinion.
Please do this by drawing a line from the box **'Your own health today'** to whichever point on the scale indicates how good or bad your current state is.

EXAMPLE



Your own health state today



Are these responses? The patient's ☐ The doctor's ☐

Name of person completing the form: _____

Date: ☐☐ day ☐☐ month ☐☐☐☐ year
(Please **PRINT** clearly)

Thank you very much for taking the time to complete this form. Please return it using the pre-paid envelope provided

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Appendix 7

Patient information booklet

Introduction to the study

You very recently had a stroke, an interruption in the blood supply to part of the brain. In some people this causes problems with eating and drinking. We believe that your nutritional status (the food and drink you take in) will have an effect on your recovery. We want to find out, firstly, whether extra food, in addition to the ward diet, is beneficial and, secondly, if you have a swallowing problem, so that you cannot eat, which is the best method of giving you nourishment, how much and when we should start this. This is why we are asking for your help, even though we know that this is a very difficult time for you.

We are studying the best methods of giving nourishment to patients after stroke in many hospitals around the country. If you agree to take part you will receive one of five different types of treatment along with the standard care for patients with stroke. If your stroke has not affected your ability to swallow, you may receive either the standard ward diet or the standard ward diet plus an energy-rich drink. If your stroke has affected your ability to swallow, you may be asked to receive liquid food through a feeding tube.

How is the treatment given and monitored?

This depends on the way food is given. If you are able to swallow you may receive an energy-rich drink which will be given to you (three times a day) along with any drugs you have been prescribed. If you are having great difficulty with swallowing, you will receive a special liquid feed via a tube; either one which is inserted into your stomach via your nose (NG Tube) or one which is inserted through your stomach (PEG Tube). Fluids will be provided by a tube placed in a vein in your arm or just under the skin in your side if there is a delay in giving you a tube feed. This liquid feed will then run through the tube during the day and/or night. Whichever treatment you receive you will be carefully monitored throughout your hospital stay. You will leave hospital when your doctor thinks that you are well enough to go home and the timing of your discharge will not be influenced by taking part in the study. In a few months, we will either send you a questionnaire to find out how you are doing or we may telephone you instead. A friend or relative may help you to complete the forms. In addition, we may telephone or write to your family doctor.

What are the risks and benefits?

Although we believe that the amount of nourishment may influence the long term problems after a stroke, some patients experience mild discomfort during tube insertion and some patients will occasionally experience serious complications related to the tube.

Who will be told about my illness?

Any information we collect about you will be confidential and used only for the purpose of this study. Information about you will only be available to research staff and the medical staff caring for you.

What happens now?

We would like you to think very carefully about whether or not to join the study. It is entirely voluntary and if you decide **not** to join, this will not influence your care in any way. You may also choose to stop taking the trial treatment at any time, although we would like to continue monitoring your progress.

And finally...

You must be happy about any decision you make and if we can give you any additional information to make the decision easier we will be happy to do so. Your family doctor will be informed about this study if you decide to join. Thank you for taking the time to read this leaflet.

If you would like to know more, please contact: _____
(or ask the nurse to contact)

Appendix 8

Consent form

The International Stroke Trials Collaboration
(Feed Or Ordinary Diet)

Consent Form

I have been fully informed of the possible risks and benefits of taking part in this study. I agree to take part in the study and understand that I can withdraw from the treatment at any time, without having to give reasons and without it affecting my future medical care.

Patient Name: _____

Address: _____

_____

Signature (Patient): _____ Date: ____/____/____
day month year

Independent Witness *(e.g. Nurse)*: _____

Address: _____

_____

If the patient gives verbal consent to take part in the trial but is unable to sign, the responsible doctor must sign here:

Responsible Doctor: _____
and the signature must be witnessed above

Assent by Another Person

I have been fully informed of the possible risks and benefits of participation in this study. I agree that _____ may take part in the study and understand that he/she can withdraw from the study at any time, without having to give reasons and without it affecting their future medical care

Signature: _____ Date: ____/____/____
day month year

Relationship with patient: _____

Address: _____

_____

Independent Witness *(e.g. Nurse)*: _____

Address: _____

_____

Please file this form in the patient's notes. DO NOT return it to the FOOD Trial Co-ordinating Centre

FOOD/C/1/898

Appendix 9

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We look forward to hearing from you.

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ISSN 1366-5278