Ketogenic Diets as an Adjuvant Therapy for Patients with Glioblastoma

Thesis submitted in accordance with the requirements of the University of Liverpool for the degree of Doctor in Philosophy by:

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DECLARATION

This thesis is the result of my own work and the material contained therein has not been presented either wholly, or in part, for any other degree or qualification.

The work for this thesis was carried out at the Department of Molecular and Clinical Pharmacology, Institute of Translational Medicine, University of Liverpool, UK and The Walton Centre NHS Foundation Trust, Liverpool, UK.

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ABSTRACT

Introduction: There is increasing interest in the use of ketogenic diets (KDs) as an adjuvant therapy for patients within glioblastoma (GBM). In animal models KDs limit tumour growth and enhance survival, but there is little evidence to support the use of KDs for patients with GBM. The aim of this thesis was to explore the feasibility of using KDs as an adjuvant therapy for patients with GBM by i) reviewing the evidence for efficacy and acceptability of KDs for patients with gliomas; ii) exploring the level of patient interest to support any future randomised controlled trial (RCT); iii) exploring the deliverability of a KD intervention in an NHS setting; iv) investigating the feasibility of a trial protocol (KEATING) and the impact this trial would have on patients with GBM, such as quality of life; and v) exploring the patient perspectives on their decision-making when invited to participate in KEATING, to inform the design of future phase III KD trials for GBM.

Methods: A systematic review was undertaken; the search strategy included seven electronic databases. Data extraction and quality assessment were undertaken for each included study. A patient survey was distributed locally and nationally to explore if there was sufficient interest in KD as an adjuvant treatment, that could be tested in a clinical trial. A scoping KD service was established to assess if the diet could be offered to adults with gliomas within an NHS setting. Following this, feasibility was assessed through a single-centre, prospective, non-blinded, randomised, pilot trial (KEATING), with an embedded qualitative study. Twelve newly diagnosed patients with GBM were randomised to the modified ketogenic diet (MKD) or medium chain triglyceride ketogenic diet (MCT KD). The diet was started during adjuvant chemoradiotherapy. The primary outcome was retention on diet; secondary outcomes included recruitment rates, dietary acceptability and completeness of data, assessed at 12 weeks and 12 months. Semi-structured interviews were conducted with a purposive sample of patients and relatives (n=15). Descriptive statistics were used for quantitative outcomes and qualitative data were analysed using thematic analysis aided by NVivo.

Results: From the systematic review no randomised trials were identified. Six case series or reports (n=39) met the eligibility criteria, all were at high risk of bias. While the review found minimal adverse events, suggesting KDs to be safe for patients with gliomas, the evidence for efficacy and acceptability of KDs was insufficient to suggest that the diet has a therapeutic effect in the management of gliomas. One hundred and seventy two surveys were completed; 66% of patients (n=114) were willing to participate in a ketogenic RCT. During the scoping service, six male patients with high grade glioma tried MKD; four of whom completed the three month intervention. MKD was deliverable within an NHS setting. KEATING achieved recruitment targets, but the recruitment rate was low (28.6%). Retention was poor; only four of 12 patients completed the three-month diet (MCT KD n=3; MKD n=1). The median duration until discontinuing the MCT KD was 38 days (36-40 days; n=2) and MKD was 39.5 days (32-49 days; n=4). Participants made instantaneous decisions without deliberation: relatives supported diet implementation. Decliners made considered decisions factoring diet burden and quality of life. Patients also sought to validate their decision by seeking the opinion of relatives. A three-month diet was undesirable to patients who declined and those who started diet and later withdrew.

Conclusion: Recruitment to a KD trial for patients with GBM is possible. To assess efficacy in a phase III clinical trial, a six week intervention period is proposed. Future trials should optimise and adequately support the decision-making of patients. The role of relatives should not be underestimated.

PUBLICATIONS AND AWARDS

Publications derived from this thesis

Martin-McGill KJ, Tudur Smith C, Marson AG, Jenkinson MD. (2018). The modified ketogenic diet in adults with glioblastoma: an evaluation of feasibility and deliverability within the National Health Service. *Nutrition and Cancer*, *70*(4), doi: 10.1080/01635581.2018.1460677.

Martin-McGill KJ, Srikandarajah N, Tudur Smith C, Marson AG, Jenkinson MD. (2018). The role of ketogenic diets in the therapeutic management of adult and paediatric gliomas: A systematic review. *CNS Oncology, 7*(2), doi: 10.2217/cns-2017-0030.

Martin-McGill KJ, Tudur Smith C, Marson AG, Jenkinson MD. (2017). Ketogenic diets as an ajuvant therapy in glioblastoma (the KEATING trial): study protocol for a randomised pilot study. *Pilot and Feasibility Studies, 3*(67), doi: 10.1186/s40814-017-0209-9.

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Awards

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LIST OF KEY ABBREVIATIONS

Abbreviation	Definition
ATRX	Alpha thalassemia/mental retardation syndrome X linked
BDA	British Dietetic Association
BCNU	Biodegradable Carmustine
BMI	Body Mass Index
CAT	Complementary and alternative therapies
CCNU	Lomustine
CHO	Carbohydrate
CKD	Classical ketogenic diet
CNS	Central nervous system
CONSORT	Consolidated Standards for Reporting Trials
ERKD	Energy restricted ketogenic diet
GBM	Glioblastoma
HGS	Hand Grip Strength
HTA	Health Technology Assessment
IF	Intermittent fasting
IHE	Institute of Health Economics
IMD	Index of Multiple Deprivation
KD	Ketogenic diet
KEATING	Ketogenic diets as an adjuvant therapy in glioblastoma trial
LCT	Long chain triglyceride
MAD	Modified Atkins diet
MAMC	Mid arm muscle circumference
MCT	Medium chain triglyceride
MCT KD	Medium chain triglyceride ketogenic diet
MDT	Multidisciplinary team
MGMT	O^6-methylguanine-DNA methyltransferase
MKD	Modified ketogenic diet
MRC	Medical Research Council
NCRI	National Cancer Research Institute
NHS	National Health Service
NICE	National Institute for Health and Care Excellent
NIHR	National Institute for Health Research
PENG	Parenteral and Enteral Nutrition Group
PFS	Progression free survival
PPI	Patient and public involvement
QLQ	Quality of life questionnaire
RANO	Response Assessment in Neuro-Oncology
RCT	Randomised controlled trial
RT	Radiotherapy
TMG	Trial Management Group
TMZ	Temozolomide
TSG	Trial Steering Group
TTF	Tumour treating fields
WCFT	The Walton Centre NHS Foundation Trust
WHO	World Health Organisation

CHAPTER 1

AN INTRODUCTION TO KETOGENIC DIETS AND GLIOBLASTOMA

1.1 THESIS OVERVIEW

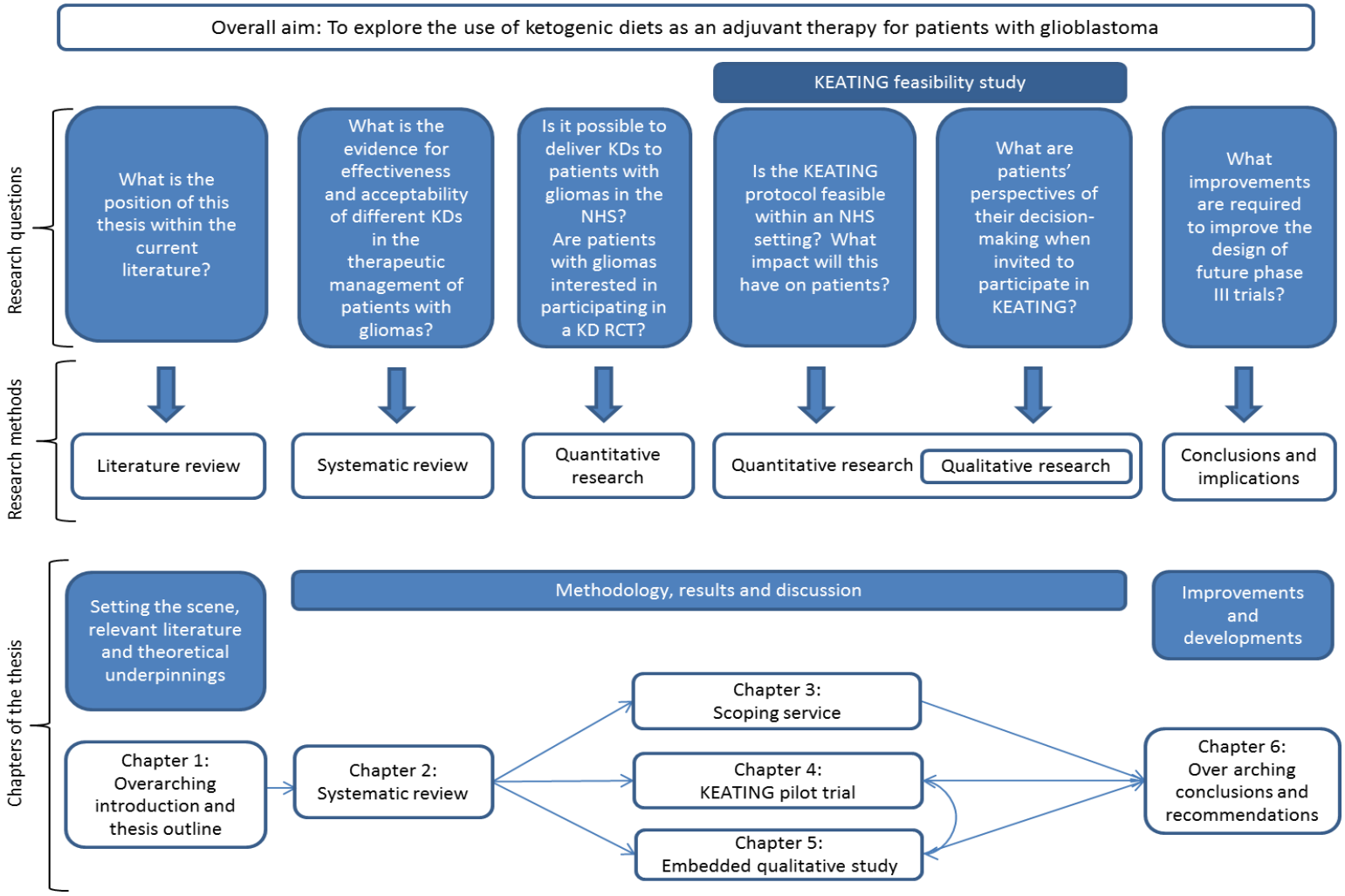
This thesis explores the feasibility of using ketogenic diets (KDs) as an adjuvant therapy for patients with glioblastoma (GBM). This research was initially motivated by patient interest in KDs locally and following the publication of The James Lind Alliance Neuro-Oncology Priority Setting Partnership which highlighted the influence of lifestyle factors, including diet, on tumour growth to be one of the top 10 research priorities for patients and researchers in the field of neuro-oncology (1).

Since the turn of the decade, KDs have been growing in popularity in the patient community, yet little dietetic support was offered across the United Kingdom (UK), due to limited evidence and a lack of funding. Therefore, in 2015 a temporary scoping service for KDs was established at The Walton Centre NHS Foundation Trust (WFCT) for patients with GBM. This service was funded for one year, with the aim of exploring if a KD service could be delivered to adult patients with gliomas in a National Health Service (NHS) setting and to assess patient demand for KD in glioma. Following the success of this project, funding was sought for a KD trial for GBM and the Ketogenic Diet as an Adjuvant Therapy in Glioblastoma trial (KEATING) was established in 2017, with the aim of assessing trial feasibility with a view to informing the design of a future phase III trial. KEATING was the first randomised, non-blinded, pilot, KD trial for patients with GBM to be undertaken in the UK and was also the first KD trial to utilise an embedded qualitative design to explore the decision-making of patients invited to participate in such trials.

This thesis begins by discussing the position of this research within the current literature (chapter 1). Chapter 2 presents a systematic review of evidence for the use of KDs in the therapeutic management of gliomas. Chapter 3 investigates patient demand for KDs in glioma populations and if an adult neuro-oncology KD service could be established in an NHS setting, concepts which were essential to understand prior to establishing KEATING. Chapter 4 presents the KEATING trial, which assessed KD trial feasibility in an NHS setting (e.g. was it possible to recruit and retain patients) and the impact of the trial on patients (e.g. quality of life, changes in body mass). Chapter 5 explores the decision-making of patients invited to

participate in KEATING through an embedded qualitative study and finally, the thesis concludes in chapter 6 by suggesting the improvements required to KEATING prior to the design of a phase III trial. A diagrammatic depiction of the thesis outline is illustrated in figure 1.1.

Figure 1: Diagrammatic depiction of thesis outline



1.1.1 CHAPTER OVERVIEW

This chapter begins by introducing the concepts of GBM and KDs, offering an overview of both areas and exploring how the two relate. A summary of the current evidence in this area will be provided, however this is limited to animal models and case series or reports (explored further in chapter 2). Given KD is a relatively new concept, its journey from epilepsy to neuro-oncology will be briefly discussed to provide context.

After discussing GBM and KDs, an introduction to the methodological approaches adopted within this thesis to explore the feasibility of using KDs as an adjuvant treatment for patients with GBM will also be presented; including methodologies utilised for the scoping service, KEATING pilot trial and embedded qualitative study. The chapter concludes by presenting the aims and objectives of the thesis.

1.2 GLIOBLASTOMA

1.2.1 Definition and prevalence of gliomas

Gliomas are malignant tumours of the glial tissue of the central nervous system (CNS) and are the most common form of primary intracranial tumour in adults, accounting for 81% of all malignant brain tumours (2). Gliomas are graded I to IV, with grade I being the least aggressive and grade IV, GBM, the most aggressive. GBMs affect 4.64 per 100,000 people each year in the UK (3).

1.2.2 Presentation

The clinical presentation of GBM can vary depending upon the location and size of the tumour (4). Patients frequently present with symptoms of raised intracranial pressure and oedema, resulting in headaches or neurological deficits. Seizures are also a common clinical presentation, with approximately 20% of patients at initial diagnosis and up to 50% of patients over the course of the disease (5).

1.2.3 Diagnosis

Gliomas are diagnosed using a combination of, magnetic resonance imaging (MRI), histopathology and molecular markers. The diagnostic and management pathway includes discussion at an integrated specialist multi-disciplinary team (MDT) meeting.

1.2.4 Classification

Historically, CNS tumours including gliomas were classified based upon their histological appearance under a light microscope. In recent years the importance of molecular profiling has become apparent and is now included in the latest World Health Organisation (WHO) classification criteria (6) and has been adopted by the National Institute for Health and Care Excellence (NICE) (7). This criteria adds objectivity to the diagnostic process of gliomas, which in turn improves determinations of prognosis and predictions of treatment response (6).

Gliomas are now presented by histopathological name followed by genetic features to provide an integrated molecular-pathology diagnosis. For GBM there are two categories; *IDH*-mutant and *IDH*-wildtype. *IDH*-mutant accounts for the mutation of the IDH gene, whilst *IDH*-wildtype refers to the lack of mutation of the IDH gene (6). Promoter region methylation of *O^6-methylguanine-DNA methyltransferase (MGMT*) is also used to categorise GBM as the methylation of *MGMT* has been associated with a predicted benefit from temozolomide

chemotherapy and improved progression free and overall survival compared to unmethylated *MGMT* patients (8). In clinical practice *alpha thalassemia/mental retardation syndrome X linked (ATRX)* gene mutations are also included in the genetic testing (7). Mutations in *ATRX* result in a loss of *ATRX* protein and are expressed in adult astrocytoma, suggesting *ATRX* loss in GBM to highlight an astrocytoma linage. Within *IDH*-mutant tumours, *ATRX* loss has indicated a better prognosis in some studies (9).

1.2.5 Clinical management

Symptomatic management of raised intracranial pressure and seizures are usually the first aspects of treatment. For patients with raised intracranial pressure, high dose corticosteroids, such as dexamethasone, are often used to alleviate the surrounding oedema and to improve some observed symptoms (10). Nearly all patients with GBM will receive corticosteroids at some point during their treatment or as the disease progresses. However, steroids are also associated with side effects such as increased appetite, increased serum glucose, fluid retention and insomnia.

For patients experiencing seizures, anti-epileptic medication is commenced. As with steroids, anti-epileptic medication is not without its side effects. These include fatigue, nausea and cognitive impairments (11). There is currently a lack of evidence to support the prophylactic use of anti-epileptic medications in this population (12), with clinical trials ongoing in this area.

Surgical resection is the second intervention in the clinical management of GBM, followed by chemo-radiotherapy. Maximal safe resection is desired as the extent to which the tumour is resected has been associated with a gradual increase in progression free and overall survival (13–15). Technological advances through surgical navigation systems, such as functional and intraoperative MRI, have improved surgical procedures by maximising resections whilst minimising deficits to neurological function; further enhancing survival and quality of life (16–18).

In some cases, surgical resections are not feasible, for example due to multi-focal disease and a biopsy is undertaken to obtain a tissue sample for molecular and histological diagnosis (7).

Following surgery, patients undergo a course of radiotherapy. Radiotherapy has been found to significantly improve the survival of patients with GBM, compared to no radiotherapy ($p<0.00001$) (19). It is offered in the form of 60Gy in 30 fractions for patients aged approximately 70 years or under with a Karnofsky performance status of 70 or more (7,16). Patients over 70 years are often treated with hypo-fractionated radiotherapy, such as 40Gy in 15 fractions, achieving similar survival benefits (19,20).

Temozolomide chemotherapy is noted to be of greatest benefit when offered concomitantly to radiotherapy at a dose of 75mg/m^2, followed by six cycles of adjuvant temozolomide (five days in every 28 days at a dose of 150-200mg/m^2) for patients aged approximately 70 years or under with a Karnofsky performance status of 70 or more (21–23). Temozolomide is also noted to be advantageous for patients with *MGMT* methylation (8) and could also be considered as concomitant to radiotherapy or alone in patients over 65 to 70 years, with *MGMT* methylation and good performance status (24,25). As a result, radiotherapy plus concomitant and adjuvant temozolomide are now considered the standard of care for most patients with GBM. For patients with a poor performance status (Karnofsky score less than 50), best supportive care is considered the most appropriate option (7,16).

Patients with GBM may develop seizures and oedema, requiring medical management through anti-epileptic drugs and steroids (dexamethasone) respectively. Whilst the medications can reduce the burden on symptoms, both can result in side effects which negatively impact patients' quality of life and are often tapered post-surgery if clinically feasible (16).

The Response Assessment in Neuro-Oncology (RANO) criteria are used to assess response to treatment through regular monitoring of MRIs and changes in clinical features (26). Clinical management in the event of recurrence is variable and can depend upon the performance status of the patient, their response to previous treatments and the patient's wishes. Treatments can include lomustine (CCNU) chemotherapy or further surgery (7). At present evidence does not support the use of bevacizumab as a monotherapy (27), but it may have potential survival benefits if offered in combination with lomustine (28).

1.2.6 Prognosis

Despite maximal safe resection, radiotherapy and temozolomide chemotherapy, overall survival for patients with GBM remains poor, with a median survival of 14 months in the UK

(3) and approximately 30% surviving beyond two years (3,21,29). Table 1.1 provides a summary of the key characteristics of *IDH*-mutant and *IDH*-wildtype GBM in relation to overall survival (6).

Table 1.1: Characteristics of *IDH*-mutant and *IDH*-wildtype GBM adapted from Louis et al. (2016)		
Characteristics	**Glioblastoma, *IDH*-wildtype**	**Glioblastoma, *IDH*-mutant**
Precursor lesion	Not identifiable	Diffuse astrocytoma Anaplastic astrocytoma
Proportion of GBM	~90%	~10%
Median age at diagnosis	~62 years	~44 years
Overall survival: Sx + RT Sx + RT + TMX	 9.9 months 15 months	 24 months 31 months
ATRX mutations	Infrequent	71%

Abbreviations: RT= radiotherapy; Sx = surgery; TMZ = temozolomide chemotherapy.

1.2.7 Treatment developments

Given the poor prognosis for these patients, the past 20 years has seen an abundance of research into new medical technologies, particularly in the development of newer chemotherapy agents and targeted therapies (30). Yet, research into new chemotherapy agents, such as bevacizumab(27), has shown little benefit to survival.

The delivery of local chemotherapy agents has also been investigated, with the development of biodegradable carmustine (BCNU) wafers (Gliadel wafers), which are implanted directly into the tumour cavity. However, a phase III trial demonstrated only a moderate improvement in survival when compared to placebo wafers (median overall survival 13.9 months BCNU; 11.6 months placebo; p=0.03) (31). There may also be a role for catheter-based, convection-enhanced delivery of chemotherapeutic agents, but this is currently undergoing phase Ib testing, with the most appropriate agent and dose yet to be established (32). Yet, this direct delivery of agents via catheters has been trialled previously and did not demonstrate any benefits in enhancing survival (33).

Targeted treatments are also growing in interest, with the role of gene therapy and molecular abnormalities being explored. A notable outcome from this being the benefit of temozolomide chemotherapy for patients with *MGMT* methylation (8). For other targeted treatments, such as cilengitide used in combination with radiotherapy and temozolomide for patients with *MGMT* methylation, no improvements in survival were noted (34). Research is ongoing into tumour associated growth factors and anti-angiogenetic strategies (30).

The hallmarks of cancer describe tumours as being immunosuppressive (35), which has seen an increase in interest in immunotherapies, particularly in the form of vaccines. As single antigens are typically only present in a sub-set of patients and so far vaccines such as rindopepitimut have demonstrated no difference in overall survival when combined with temozolomide (20.1 months) compared to temozolomide alone (20.0 months) (36), combinations of tumour-associated antigens have been explored, demonstrating positive signs towards promoting survival (30). However, data for combination vaccines is limited to phase I clinical trials, is underpowered to test effectiveness and patients still experience side effects and toxicities (37,38). As with chemotherapeutic agents, there may also be a role for nanotechnology in aiding the delivery of immunotherapeutic agents in overcoming the obstacle of the blood brain barrier of CNS tumours (39).

Whilst demonstrating some promise, these new and exploratory therapies target specific pathways or specific sub groups of patients and the reasons for the lack of progress are multifactorial but include the marked tumoural heterogeneity, the development of treatment resistance and the challenges of delivering drugs across the blood-brain barrier. One exception to this is the newly developed tumour treating fields (TTF) device Optune®, which adopts a broader approach compared to targeted therapies and has demonstrated clinical effectiveness in combination with temozolomide compared to temozolomide alone (median overall survival 20.5 months TTF and temozolomide; 15.6 months temozolomide alone; p=0.004)(40), whilst maintaining quality of life (TTF and temozolomide compared to temozolomide alone p<0.01), in patients with newly diagnosed GBM (41). Despite illustrating clinical effectiveness, TTF technology is yet to demonstrated cost-effectiveness, with an incremental cost-effectiveness ratio of €549, 909 per life year gained (42), hence it is currently not recommended by NICE (43).

Due to the lack of treatment options and the limited success of clinical trials, alternative treatment options are being explored and the James Lind Alliance Priority Setting Partnership reports the effect of lifestyle factors, including diet, on tumour growth to be a top 10 research priority for the neuro-oncology community (1).

1.3 DIET AND ONCOLOGY

Diet has a dual role in oncology. Firstly, diet can have a causative or protective effect in influencing cancer development. For example, a high fibre intake is associated with reduced risk of bowel cancer (44). Secondly, diet is viewed as an essential component of cancer care post diagnosis with the location of the cancer usually dictating the nutritional implications and subsequent management. For example, cancers of the gastrointestinal tract are likely to lead to malnutrition and cachexia due to impaired absorption, reduced dietary intake and the pronounced side effects of treatment, which could result in the prophylactic placement of enteral feeding tubes.

In gliomas, large scale prospective evidence shows little, if any, association between diet and glioma risk (45). Despite treatment involving surgery, radiotherapy and chemotherapy, patients usually experience little, if any, nutritional consequences beyond radiotherapy related fatigue and steroid induced weight gain. Consequently, the current dietary recommendations for patients with GBM are based upon national healthy eating guidelines (46,47), with referral to a dietitian for bespoke advice for patients at risk of malnutrition (48).

In recent years, there has been a growing interest in the use of nutrition based complementary and alternative therapies (CATs), with up to 75% of patients with cancer using CATs during the course of their treatment, despite little evidence illustrating efficacy or safety (49). In neuro-oncology, this interest has focused upon KDs for patients with GBM and has been driven forward by both research and patient communities.

1.4 KETOGENIC DIETS

KD is an 'umbrella term' used to describe high fat, low carbohydrate, adequate protein diets which promote the utilisation of fat for energy, in the form of ketones, thus reducing the requirement for glucose and mimicking fasting metabolism.

1.4.1 History of ketogenic diets

The use of KDs stems back to biblical times when fasting was noted to relieve epileptic seizures (Matthew 17:21) (50). However, the first medical reference of fasting to aid seizure management was noted in 1911 (51). Long term fasting had health limitations, therefore, in 1921 KDs were developed to mimic the ketotic effect of fasting whilst maintaining a

nutritional intake (52). The dietary intervention was popular for the management of epilepsy until antiepileptic drugs were developed in the late 1930s, when it fell out of favour.

In the mid-1990s, KDs resurged in popularity due to increasing interest from parents who wished to reduce the epileptic drug burden for their child or to explore new avenues due to drug-resistance. Since then, several randomised controlled trials (RCTs) have proved effectiveness of the diet in children with drug-resistant epilepsy (53) and KDs are a recommended treatment for drug-resistant paediatric epilepsy by NICE (54). The KDs traditionally used in the management of drug-refractory paediatric epilepsy are described in table 1.2 (55).

Table 1.2: A comparison of KDs used in the management of drug-resistant epilepsy in the UK (55–59)

Dietary element	**CKD (e.g. 4:1)**	**MKD**	**MCT KD**	**MAD**
Carbohydrate (excluding fibre)	4% ETER	15-30g/d or 5% ETER	15-18% ETER	10-20g/d
Fat	90% ETER	60-80% ETER	72-75% ETER (30-60% MCT)	Ab lib
Protein	6% ETER	Ab lib	10% ETER	Ad lib
Food measurements	Weighed	Weighed/ household measures	Weighed	Visual

Abbreviations: CKD = classical ketogenic diet; MAD = modified Atkins diet; MCT KD = medium chain triglyceride ketogenic diet; MKD = modified ketogenic diet; ETER = estimated total energy requirement; ratio 4:1 = 4g of fat to 1g of carbohydrate and protein combined.

In recent years, interest in KDs has grown in clinical conditions other than epilepsy, with pre-clinical evidence in gastric cancer (60), colon cancer (61,62), Motor Neurone Disease (MND) (63) and traumatic brain injury (64,65) demonstrating positive effects. Clinical evidence from pilot studies has also been generated for children with autism spectrum disorder (66) and adults with Alzheimer's Disease (67), Parkinson's disease(68), migraine (69) and lung and pancreatic cancer (70). However, the area generating most interest is GBM.

1.4.2 Ketogenic diets in glioblastoma therapy

The interest in KDs for aiding the management of GBM stems from the alterations in the metabolism of cancer cells, with an up regulation of glycolysis regardless of the availability of oxygen; a discovery made in 1927, the so-called 'Warburg effect' (71). KDs were hypothesised to work by exploiting the 'Warburg effect' through reducing the availability of

dietary glucose and increasing the availability of ketone bodies. These ketone bodies can be readily used for energy by the body, but less readily utilised by the tumour, theoretically slowing growth (72–75). A systematic review and meta-analysis of the antitumor effects of KD in mice demonstrated prolonged survival compared with standard diet (mean survival time ratio = 0.85 [95% highest density interval = 0.73, 0.97]; hazard ratio = 0.55 [95% highest posterior density interval = 0.26, 0.87]) (76).

Recently, new theories have explored other mechanisms of action for KD in GBM, with ketone bodies and medium chain triglyceride (MCT) fats playing a role in tumour metabolism, rather than or in addition to a reduction in glucose. Laboratory studies in GBM cell lines have shown ketone bodies in the absence of glucose restriction to exert growth inhibition, then, when combined with chemotherapy (Carmustine, BCNU) these effects are amplified when compared to BCNU or ketones alone (77). This is further supported by mouse models of malignant glioma, whereby KD given alongside temozolomide enhanced survival compared to temozolomide alone (78). The same authors also illustrate the role KDs have in potentiating the effects of radiotherapy, with animals living significantly longer when compared to radiotherapy alone (79). Animal models also illustrate KDs to have positive effects on reducing peri-tumoural oedema (80) and in reducing tumour angiogenesis (73). Thus KDs are viewed to have a broad scope in the possible management of GBM.

MCT fats can be incorporated into KDs; creating the MCT KD which is readily used in the management of paediatric epilepsy (see table 1.1.). The use of MCT in oncology models is also growing in popularity for numerous reasons. Firstly, MCT offers the benefit of increased ketone production (per calorie of energy) compared to long chain triglyceride (LCT) fats due to their rapid absorption into the portal system (81) (82) . Secondly, due to raised ketone levels, slightly more carbohydrate can be included in the diet, which improves palatability. Thirdly, MCT has an anti-inflammatory effect compared to LCT fats (83). Finally, various oncology animal models have illustrated MCTs to inhibit tumour growth and increase survival, compared to classical KDs containing LCT (60,61,83,84). Interestingly, the role of C8-MCT has been illustrated to be of greater benefit than C10-MCT at inhibiting tumour growth (83). Therefore, the type of fat could also play a role in the mechanism of action of KDs.

Whilst the results appear promising, animal models have limitations. The 'dosing' of the KD used in most models is much higher than a KD that can be tolerated in humans, such as a 8:1 KD in mice versus 4:1 in humans (i.e. 8g fat to 1g carbohydrate and protein combined). The pharmacokinetics is also likely to differ between animal models and humans. With the exception of Scheck et al.,(79) the animal models do not follow the standard treatment pathway experienced by patients, such as radiotherapy and chemotherapy, which appears to influence the potential effects of KDs. In many studies, KD is also commenced at tumourgenesis which is not replicable in patients. Studies are further limited by small sample sizes and heterogeneity (76). Thus, further research is required to fully understand the mechanism of action of KDs in GBM, including the effect of KDs and ketone bodies on the blood brain barrier (85).

In patients with gliomas, the evidence for KD is limited to case studies and case reports. This research is presented in chapter 2 and has been published elsewhere (86). To summarise, the use of a KD for patients with a glioma was first reported in 1995 when two children commenced MCT KD as an adjuvant to standard treatment (87). Six studies have been published in total; all utilising different KDs at different time points in the treatment pathway (KD initiated at diagnosis; KD initiated at recurrence). No studies have investigated the influence of KDs on anti-epileptic medications or corticosteroids in GBM populations. Interestingly, one retrospective, pilot study found corticosteroids to be safe in conjunction with a KD for patients with epileptic encephalopathies (88).

From epilepsy literature, KDs are known to have reported side effects, predominantly short term gastrointestinal issues at dietary initiation, such as constipation and diarrhoea (53). Other side effects reported in a small numbers of patients include pancreatitis, gall stones, weight loss and decreased bone matrix density (53). Whilst the stricter KDs, such as classical KD, may attain superior results in relation to effectiveness, they are associated with a greater number of side effects when compared to less restrictive KDs, such as MAD (53).

KDs can also result in altered lipid profiles; however a prospective study has illustrated the cardiovascular safety of MAD for 12 months in adults with epilepsy (89). Further research is required to understand the cardiovascular effects of stricter KDs and the long term side effects of these dietary regimes (89).

Whilst KDs appeared to be safe, the acceptability and efficacy of a KD intervention for patients with GBM remained to be investigated.

1.5 AN INTRODUCTION TO THE THESIS METHODS

The use of KD in the therapeutic management of GBM was a relatively new concept and in its infancy. Prior to designing and launching a RCT in this area, it was important to understand patient demand, service deliverability and trial feasibility within the NHS setting. Patient demand and service deliverability were explored through a survey and scoping service, following which trial feasibility was explored in KEATING and an embedded qualitative study.

1.5.1 Scoping service and survey

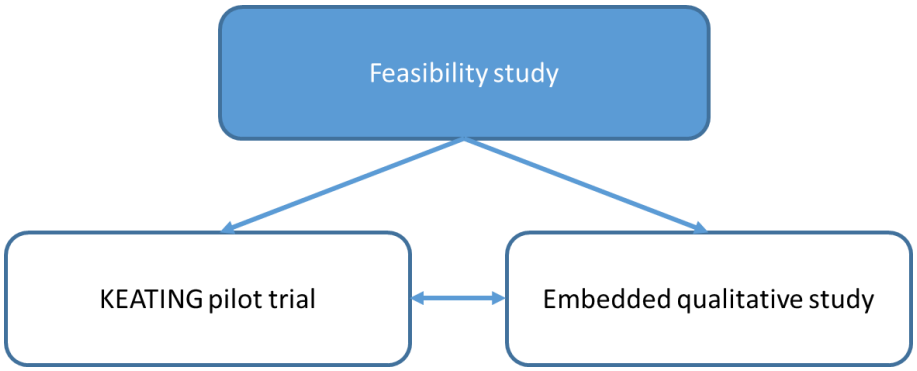
When first embarking on using KDs in neuro-oncology attitudes of patients with gliomas towards KDs had yet to be explored and it was unknown if there would be sufficient interest within the glioma community to support a KD trial. Therefore, a quantitative survey was developed by a multi-disciplinary research team, to provide insights into patient demand for this potential healthcare intervention (90,91). This was distributed on a local and national scale.

It was also important to understand if KDs could be delivered to adult patients with high grade gliomas in NHS hospitals. At the time the only funded services were for paediatric epilepsy. The experience of establishing a new NHS service for adult neuro-oncology would provide essential learning opportunities if a trial were to be used in the future as a means to develop new KD services in recruiting sites. Whilst animal models have illustrated KDs to be most beneficial when offered alongside radiotherapy, it was unknown where in the treatment pathway patients would follow the diet (e.g. pre-treatment, at recurrence) and to whom the diet would appeal. Thus, a temporary scoping service was established at WCFT.

1.5.2 Feasibility study

A feasibility study was undertaken to explore KDs as an adjuvant therapy for patients with GBM. This involved a pilot trial (KEATING; section 1.5.3) and an embedded qualitative study (section 1.5.4).

Figure 1.2: Ketogenic diet feasibility study for patients with glioblastoma (adapted from O'Cathian, 2018 (92))



1.5.3 KEATING pilot trial

The use of the term 'pilot study' is widespread and has a multitude of meanings in clinical research. For the purpose of KEATING, 'pilot study' refers to a preparatory study designed to investigate the capabilities of study design, recruitment feasibility, barriers to study completion, acceptability of the intervention to patients, time required for study participation, estimates of missing data and attrition, and protocol refinements to enable the development of future studies (93,94). Given the lack of previous research, assessing such parameters via a pilot study was essential prior to designing a phase III KD clinical trial for GBM.

For KEATING a prospective, non-blinded, randomised pilot study design was selected to mirror the study designs of future RCTs. As it was unknown which KD, if any, would be effective in GBM management, two KDs previously noted within the literature were selected for KEATING. A control arm was not used at this stage as the acceptability, tolerability and feasibility of KDs alongside standard treatment were being explored, rather than the feasibility of randomisation between diet and no diet. A multi-arm multi-stage trial design was considered for the inclusion of a control arm (95,96), however the sample size required to run such a study was beyond that which could be achieved by a single site and beyond the scope of this thesis.

Over time, KEATING experienced issues with recruitment and retention of diet. Hence, a qualitative study was embedded to explore patients' decision-making when invited to participate in the trial.

1.5.4 Embedded qualitative study

Qualitative research is becoming increasingly useful within clinical trials as an embedded component. It can be useful to explore uncertainties which may impact the success of clinical trials, such as recruitment, retention, study and intervention acceptability, implementation and practicality, rich data on which is difficult to obtain by quantitative means (97).

Qualitative methods can be utilised before, during or after a clinical trial, to optimise trial design and practises with a view to enhancing participant experience and trial success through the generation of theory and models to guide intervention development (98). When situated prior to a trial, qualitative methods are used to inform trial design, by addressing uncertainties and barriers raised by trial stakeholders, such as participants or clinicians to enhance the acceptability of trial procedures (97). When embedded and used during a clinical trial, qualitative methods can assess the feasibility and deliverability of the intervention (99), explore knowledge and understanding of trial methods (such as informed consent, decision-making, randomisation) and aid understanding of the participants perceptions of processes related to implementation and change (100). After a clinical trial, qualitative research can be used to further interpret the findings of the trial, explain variations in results, explore the participants' experiences of the trial and participants' views regarding acceptability of the study intervention (98,100).

Whilst there is an abundance of literature regarding the decision-making of patients involved in drug trials, there is little literature exploring the decision-making of incurable oncology populations in feasibility or early stage clinical trials, especially for dietary interventions. Qualitative studies have been successfully embedded into diet-oncology trials for breast and prostate cancers over recent years, exploring the feasibility and acceptability of dietary and lifestyle interventions, along with recruitment challenges and patient experiences (101–107). It is difficult to extrapolate these results to a KD trial for patients with GBM given the disparities in survival and the interventions.

Prior to KEATING, KDs had yet to be explored by qualitative means, either in the context of a trial or within clinical practice (including other conditions such as epilepsy). Therefore this qualitative study was the first to explore patients' experiences of KDs and their decisions to enter into and continue to participate in the trial, enabling the design of bespoke strategies to optimise informed consent and patient experience in future trials.

1.6 THESIS AIMS AND OBJECTIVES

Aim:

- To explore the feasibility of using KDs as an adjuvant therapy for patients with GBM.

Objectives:

- To review the evidence for efficacy and acceptability of different KDs in the therapeutic management of patients with gliomas.
- To explore the level of interest from patients with gliomas to support a KD RCT.
- To explore if KDs can be delivered to adult patients with gliomas in an NHS setting.
- To investigate if the KEATING protocol is feasible within an NHS setting and what impact this will have on the health of patients with GBM.
- To explore patients' perspectives of their decision-making when invited to participate in KEATING.
- To recommend improvements to optimise future phase III study design.

CHAPTER 2

A SYSTEMATIC REVIEW OF THE EVIDENCE FOR THE USE OF KETOGENIC DIETS IN THE THERAPEUTIC MANAGEMENT OF GLIOMAS

2.1 CHAPTER OVERVIEW

This chapter discusses the existing evidence for the use of ketogenic diets (KDs) in the therapeutic management of gliomas. A systematic review and meta-analysis investigating the systemic anti-tumour effects of KDs in mice demonstrated a prolonged survival for the KD groups compared to standard diet (mean survival time ratio [MR] = 0.85 (95% highest posterior density interval = [0.73, 0.97]) and hazard ratio = 0.55 (95% highest posterior density interval [HPDR] = [0.26, 0.87])) (76). Interestingly, KD was less effective in the brain tumour subgroup (MR = 0.89, 96% HPDR =0.76, 1.04), with the brain tumour model selecting a later starting point for KD (at least one day after tumour initiation), accounting for 26% of the heterogeneity, rather than initiating KD at tumourgenesis as conducted in the systemic cancer models (76).

However, no such systematic review or meta-analysis existed for human studies. For studies of GBM in patients, different types of KDs are utilised at different time points in the treatment pathway and it was not known which KD, if any, was effective and which carried the greatest burden for the patient. Therefore, this systematic review not only assessed efficacy, but also quality of life and adverse events for the different diets.

The chapter follows published guidance for the conduct of systematic reviews (108) and begins by presenting the aims of the review and methodology adopted. The results include a risk of bias assessment, a summary of the effects of the intervention and of ongoing clinical trials in the field of KD and glioma. Finally, the quality and acceptability of the evidence are discussed, concluding with implications for future practice and research.

2.2 INTRODUCTION

2.2.1 Scoping search

A scoping search was undertaken to aid the development of the research question. Data collection categories included authors, year of publication, study location, study design, dietary intervention, study population and outcomes (109).

From the results there appeared to be a small, but adequate, volume of evidence available from which to undertake a systematic review. No randomised controlled trials (RCTs) were identified for the use of KDs in gliomas in humans; however, a range of other study designs were identified.

2.2.2 Research question and aim

Is there a role for KDs in the therapeutic management of adult and paediatric gliomas?

Aim: To review the evidence for efficacy and acceptability of different KDs in the therapeutic management of patients with gliomas.

2.3 METHODOLOGY

The protocol for this systematic review was registered with PROSPERO (identification number: CRD42017056752).

2.3.1 Inclusion criteria

The inclusion criteria are illustrated in table 2.1 using the PICO method.

Table 2.1: A PICO table illustrating review inclusion criteria.		
Population	Adults and children with glioma tumours following a KD.	
Intervention	Any form of KD, with KD defined as a diet that is designed to produce ketones.	
Comparator	Other KDs or control diet thought to have no effect on gliomas*.	
Outcomes	Objective or self-reported measures are acceptable for the following outcomes:	
	Primary outcomes: • Overall survival • Progression free survival	Secondary outcomes: • Adverse events • Retention rates • Quality of life • Acceptability • Tolerability • Compliance • Duration of KD • Time of dietary commencement (in relation to treatment pathway) • Ketone levels • Glucose levels
Setting	Primary, secondary or tertiary healthcare. Inpatient, outpatient or community settings.	
Study design	All.	

*A comparator diet is unlikely to be identified following the results of the scoping search, therefore a comparator is not essential to the inclusion criteria and all study designs are permitted.

No restriction was placed on year of study or publication status. The search was limited to English language publications.

2.3.2 Search strategy

A four part search strategy was implemented to identify suitable studies for the review.

2.3.2.1 Electronic searches

The following electronic databases were searched:

1. EMBASE
2. PubMed
3. Cochrane Library
4. CINAHL Plus
5. MEDLINE
6. SCOPUS
7. Web of Science

This search was undertaken on 25th January 2017, with updates identified until 18th August 2017. An example search strategy can be found in appendix A.

2.3.2.2 Hand searches

References from literature included in the review were hand searched to identify other possible studies.

2.3.2.3 Study registries

The following study registries were searched:

1. ClinicalTrials.gov
2. The World Health Organisation International Clinical Trials Registry Platform
3. UK Clinical Trials Gateway
4. International Standard Randomised Controlled Trial Number Register (ISRCTN)
5. National Institute of Health Clinical Trials Registry
6. National Research Register Projects Database Achieve
7. PROSPERO

This search was undertaken on 21st March 2017, with updates identified until 18th August 2017.

2.3.2.4 Other resources

Conference abstracts and posters were included in the search to identify ongoing or recently completed studies.

2.3.3 Screening and selecting

2.3.3.1 Duplicate references

Duplicate references were removed from the search results using Mendeley© reference manager (Elsevier, London, UK) and manual searching.

2.3.3.2 Inclusion criteria pilot

An inclusion criteria pilot was undertaken using the below tool (table 2.2) to screen titles and abstracts to identify full text papers suitable for inclusion in the review. The tool was piloted on 30 articles (108), no alterations were required.

Table 2.2: Inclusion criteria screening tool (108)		
Review question: Is there a role for KDs in the therapeutic management of adult and paediatric gliomas?		
Aim: To review the evidence for efficacy and acceptability regarding the effects of different KDs in the therapeutic management of patients with gliomas.		
Reviewer initials:		**Date:**
Author:		**Year:**
Title:		**Journal:**
	Include	**Exclude**
Population	☐ Adults or children with glioma	☐ Adults and children with other cancers
Intervention	☐ Ketogenic diet	☐ Other diets
Comparator	☐ None required	☐ n/a
Outcomes	☐ Survival (overall or progression free) May also include: ☐ Adverse events ☐ Retention rates ☐ Quality of life ☐ Type of KD ☐ Duration of KD ☐ Time of dietary commencement ☐ Compliance ☐ Acceptability ☐ Tolerance ☐ Ketone levels ☐ Glucose levels	☐ No survival
Study design	☐ Any	☐ n/a
Overall decision	☐ INCLUDED	☐ EXCLUDED
Notes		

2.3.3.3 Screening of included studies

Inclusion criteria were applied to titles and abstracts identified in the search results. For those studies identified for potential inclusion full text was obtained and inclusion criteria reapplied. Screening was conducted by one author (KJM), with a second author cross checking 10% of the screening (NS).

Following this, an expert in the area (Dr Adrienne C Scheck, Associate Professor, Dignity Health, Phoenix, USA) was contacted to ensure all relevant studies were obtained and to identify if any current studies were shortly due for completion or publication.

2.3.3.4 Reporting results of searches

Records of search methods were maintained to allow for replication and update searches to be undertaken. The following information was recorded (108):

- Date search undertaken
- Database version and interface used
- Search terms for each individual search

A PRISMA flow diagram was then be adopted to document the number of references located from databases searched and other sources, number of duplicates removed, records screened, records excluded, full text articles screened, full text articles excluded with reasons and the number of studies included in the final review (110).

2.3.4 Data extraction

Data extraction was undertaken by two authors independently (KJM and NS). Discrepancies were discussed between the authors in the first instance. Any disagreements were resolved by discussion. A third author (MDJ) was available for consultation if required.

A data extraction form was used to standardise the procedure. This form was piloted on two of the included studies, following which the data extraction tool was adapted to specify duration of intervention (mean, median and range), duration of follow up periods and to clarify language.

Types of data extracted included descriptive data; study characteristics (author, publication year, full paper/ abstract, location, funding, study design, duration of study, dietary intervention, dietary duration, dietary commencement, follow up period), population characteristics (mean age, gender, previous treatment, number of participants), and analytical data (overall survival, progression free survival, adverse events, retention rates, quality of life, compliance, tolerance, ketone level, glucose level).

In the event of missing data, the author(s) were contacted via email.

It was not possible to conduct a meta-analysis due to the heterogeneity of the methods and interventions of the included studies, therefore effect size could not be established (without bias). This was assessed by two of the review authors (KJM and NS).

2.3.5 Quality assessment

All study types were permitted for inclusion in the review, yet only case studies and case series were identified. Thus, the Institute of Health Economics (Canada) Case Series Quality Appraisal Checklist was selected as the appropriate quality assessment tool (111)(see appendix B). The tool was updated to include assessor annotations specific to this review as recommended by the tools authors (111).

The quality assessment tool was piloted on two studies to ensure suitability. Two authors (KJM and NS) independently quality assessed each study and then compared results to identify any conflicting evidence. All disagreements were resolved by discussion. Quality assessment took place after data extraction to minimise reporting bias. Results of this exercise were tabulated. It was not possible to assess the confidence of cumulative evidence as the evidence is based on case series, for which no scale existed to the authors' knowledge.

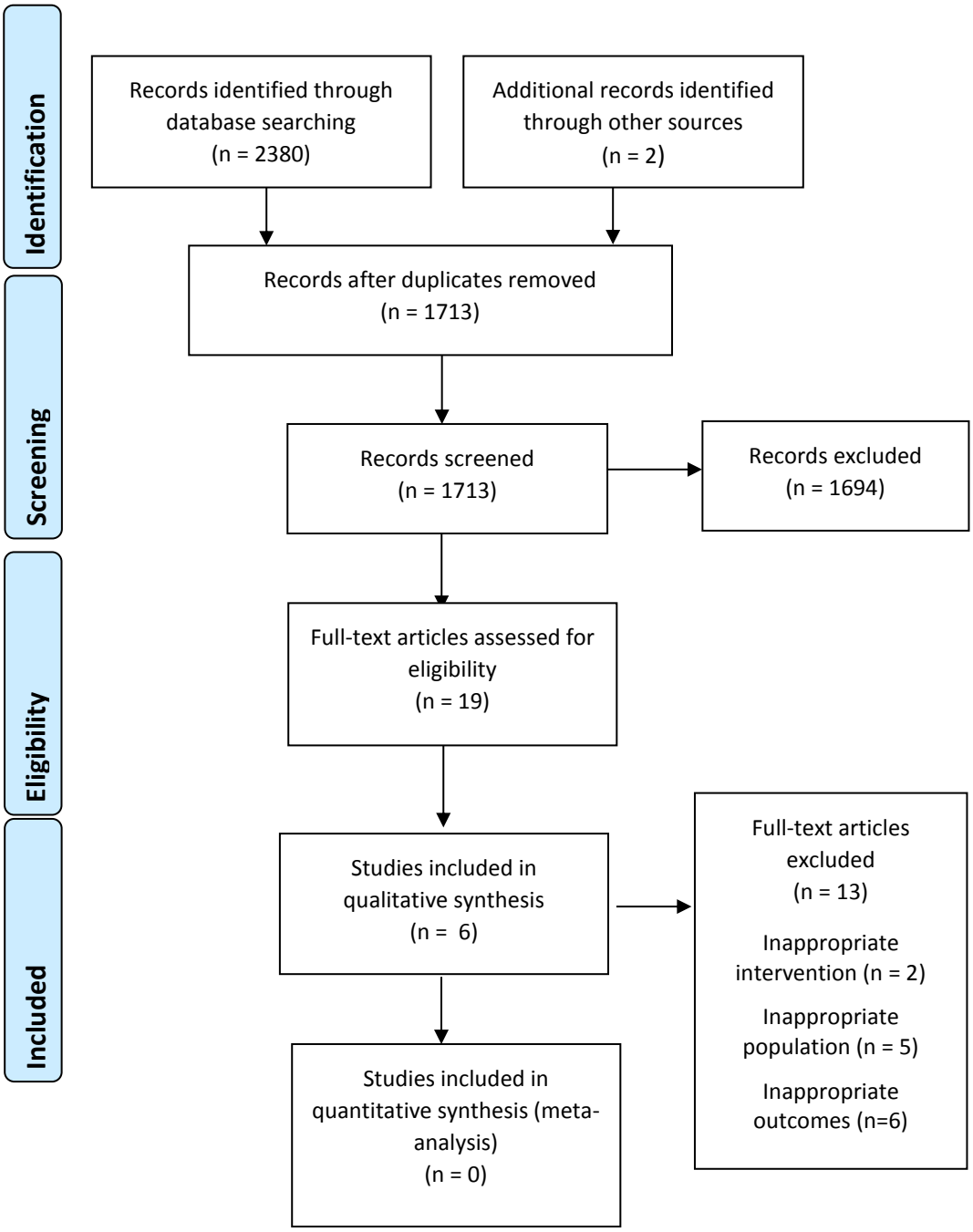
2.4 RESULTS

2.4.1 Description of studies

2.4.1.1 Results of the search

Following the search strategy cited above 2380 records were identified, along with two additional records identified through other sources (hand searches of included references). After removing duplicates 1713 records remained. Following the screening of records 19 remained eligible for inclusion. These studies underwent a full text review, following which a further 13 studies were excluded due to inappropriate interventions (112,113), inappropriate populations (114–118) and inappropriate outcome measures (119–123). Six studies met the eligibility criteria for this review (87,124–128). Figure 2.1 illustrates the search results.

Figure 2.1: PRISMA flow diagram



2.4.1.2 Included studies

Six studies have been published since 1995, conducted in the USA and Europe. Of the six studies, one study was a retrospective case report (128), two retrospective case series (124,127), two prospective case reports (87,126) and one prospective case series (125). One study was conducted in paediatrics (87) and five in adults (124–128). Population sample size varied between one and 20 participants. A variety of KD interventions were used, ranging from energy restricted KD (126,128), MAD (127), MCT KD (87) and 50 to 60g carbohydrate KDs (124,125). Dietary duration ranged from one to 24 months. Table 2.3 provides a summary of the study characteristics. Further details can be found in appendix C.

2.4.2 Risk of bias in included studies

All six studies were quality appraised for internal validity. No study met all quality assessment criteria set out by the Institute of Health Economics (Canada) Case Series Quality Appraisal Checklist (129). A summary of quality assessment of included studies can be found in table 2.4. For further details refer to characteristics of included studies tables (appendix C).

Table 2.3: Study characteristics										**Survival data (median [range])**	
Study	**Methods**	**Primary objective**	**Number of patients**	**Age** (yrs)	**Diagnosis**	**Dietary intervention**	**Dietary commencement**	**Dietary duration** (months, [range])	**Follow up** (months, [range])	**Overall survival**	**Progression free survival**
Champ et al., 2014 (USA)	Retrospective case series	Safety	n=6	34-62	Grade III-IV glioma	50g CHO KD	Post Sx prior to RT/ TMZ	3-12	5-20.3	27-88 weeks (range only)	45 weeks (median only)
Nebeling et al., 1995 (USA)	Prospective case report	Nutritional status, tumour metabolism and QoL	n=2	3-8.5	Grade IV anaplastic astrocytoma spinal cord; grade III cerebellar astrocytoma	MCT KD (60% MCT, 20% CHO)	Post treatment	2-14	2-24	0 deaths reported	0 progressions reported
Rieger et al., 2014 (Germany)	Prospective case series	Safety and tolerance	n=20	30-72	GBM	60g CHO KD, fermented yoghurt drinks, two plant oils	At recurrence	2-8	1.2 (median only)	32 weeks (6-86+ weeks)	5 weeks (3-13 weeks)
Schwartz et al., 2015 (USA)	Prospective case report	Unclear	n=2	52-55	GBM	ERKD (80% TER), 3:1	Post treatment	1-3	1-3	No data	8 weeks (4-12 weeks)
Strowd et al., 2015 (USA)	Retrospective case series	Safety and clinical impact	n=8	28-54	Grade II-IV glioma	15-20g CHO MAD	Post treatment	2-24	13.2±8 (mean, S.D.)	0 deaths reported	No data
Zuccoli et al., 2010 (Italy)	Retrospective case report	Unclear	n=1	65	GBM	ERKD (600kcals), 4:1	Post Sx prior to RT/ TMZ	1.8	25	No data	43 weeks

Abbreviations: CHO= carbohydrate; ERKD= energy restricted ketogenic diet; GBM= glioblastoma; KD = ketogenic diet; MAD= modified Atkins diet; MCT = medium chain triglyceride; QoL= quality of life; RT= radiotherapy; S.D= standard deviation; Sx= surgery; TER= total energy requirements; TMZ = temozolomide; USA= United States of America; Yrs= years. Definitions: Post treatment defined as post-surgical resection, radiotherapy and concomitant chemotherapy (full details see appendix C).

Table 2.4: Summary of quality assessment of included studies

	Objectives	**Design**			**Population**			**Interventions and co interventions**		**Outcome measure**				**Statistical analysis**	**Results and conclusions**					**Competing interests**
Study	Aim/ objectives	Prospective	Multicentre	Consecutive recruitment	Participant characteristics	Eligibility criteria	Similar point of trial entry	Clear intervention	Clear additional interventions	OM established priori	Blinded assessors	Appropriate methods	OM pre and post intervention	Appropriate tests	Follow up period	Losses reported	Estimates of random variability	AE reported	Supported conclusions	Reported upon
Champ et al., 2014	✓	✗	U	✓	✓	✓	✓	✓	✓	✓✗	U	✓	U	U	✓	✓	✓✗	✓	✓	✓
Nebeling et al., 1995	✓	✓	✗	U	✓	✗	✗	✓	✓	✓	U	✓✗	U	U	✓	✓	✗	✓	✓	✓
Rieger et al., 2014	✓	✓	✗	✓	✓	✓	✓	✓	✓	✓	U	✓✗	U	✓	✓	✓	✓	✓	✓	✓
Schwartz et al., 2015	✓✗	✓	✗	U	✓	✓	✓	✓	✓	✓✗	U	✓	✓	U	✓	✓	✗	✓	✓	✓
Strowd et al., 2015	✓	✗	✗	✓	✓	✓✗	✓	✓	✓	✗	U	✗	U	✓	✓	✓	✓	✓	✓	✓
Zuccoli et al., 2010	✗	✗	✗	U	✓	✗	U	✓	✓	✗	U	✓✗	U	NA	✓	✓	✗	✓	✓	✓

Abbreviations: OM = outcome measure(s), AE = adverse events, ✓ = yes (item adequately addressed), ✗ = no (item not adequately addressed), ✓✗ = partial (item partially addressed), U = unclear, NA = not applicable.

2.4.3 Effects of interventions

A summary of the outcomes listed below can be found in table 2.5.

2.4.3.1 Critical outcomes

Overall survival

Four studies (n=36) reported overall survival (87,124,125,127). Follow-up ranged from six to 91 weeks. Two studies comprising of 10 patients reported no deaths (87,127). Two studies comprising of 22 patients reported survival ranging from six to 88+ weeks (125,126). Overall survival can be related to diagnosis and dietary intervention in table 2.3.

Progression free survival

Five studies reported progression free survival (PFS) (n=30). Time to progression ranged from three to 45 weeks in four studies (124–126,128). One study comprising of two patients reported no progression following 62 weeks on diet at the time of publication (n=1), however PFS for the second patient was not reported. PFS can be related to diagnosis and dietary intervention in table 2.3.

2.4.3.2 Important outcomes

Adverse events

All studies reported adverse events (n=39). The most frequently reported adverse events related to KD interventions were weight loss (124–128)), ranging from -2.2% (125) to -13% body weight (128) and increased cholesterol (87,126). Other adverse effects reported in low numbers were deep vein thrombosis (124), grade III leukopenia (125), lymphopenia (128), hyperuricemia (128), hypoproteinemia (87).

Dietary retention rates

The retention rate could be determined for three studies (n=24), all of which were undertaken prospectively using a defined protocol, with retention ranging from 50-100% (87,125,126)]. Retention was determined at eight weeks (n=2) (87)], 12 weeks (n=2) (126)] or at point of tumour progression (n=20) [22] (median PFS 5 weeks, range 3-13 weeks). Reasons for withdrawal from diet included tumour progression (n=1) (126)] and negative impact on quality of life (n=3), but no validated tool was documented (125).

Quality of life

No studies reported upon quality of life using the appropriate objective or subjective measures.

Acceptability

No studies reported upon dietary acceptability using the appropriate objective or subjective measures.

Tolerability

Two studies reported dietary tolerability (n=18). Grade I constipation was reported at dietary initiation (n=2), grade I fatigue (n=4) during radiotherapy and grade II fatigue (n=1) during 30% energy restricted 30-50g carbohydrate KD (124). Gastrointestinal assessment reported diarrhoea at a mean intensity of <1 (weak), constipation at a mean intensity of <1 (weak), hunger of mean intensity of >1 but <2 (weak to moderate) and demand for glucose mean intensity of >1 but <2 (weak to moderate), using a non-validated questionnaire (n=12) (125).

Compliance

Three studies reported upon dietary compliance (n=24). Maintenance of ketosis was used as a surrogate for compliance in two studies (87,126), whilst patient self-reporting was used in the remaining trial and indicated compliance for 6.8 days per week (n=20) (125).

Ketone levels [1]

Five studies reported ketosis (n=24). Three studies reported serum ketosis (n=6), with levels of 0.3mmol/L* to 7mmol/L (n=4) (124,126) and maintenance of serum ketosis was reported by one study (n=2) (87). Urinary ketosis was reported by two studies (n=14). One study reported urinary ketones between 1.5-2.5mmol/L during first three weeks of diet (n=1) (128). In the other, urinary ketosis was achieved at least once in 92% participants (n=12/13) and when assessing all urinary measurements from 12 participants, ketonuria was present in 73% of cases (125). Methodology and frequency of testing was not consistent between studies.

Glucose levels [2]

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[1] * indicates reported units have been converted to mmol/L from mg/dl for comparison.

[2] * indicates reported units have been converted to mmol/L from mg/dl for comparison.

Five studies reported serum glucose levels (n=18). Three studies (n=14) reported a decrease in serum glucose during diet compared to pre diet levels. Levels varied from a mean non fasting serum glucose of 7.9mmol/L* pre diet (no S.D.) to 4.7mmol/L* (no S.D.) (n=4) (124), to 7.5mmol/L pre diet decreasing to 3.5mmol/L during diet (n=1) (128), with a less extreme response noted in one study (5.5±1.2mmol/L* pre diet to 5.1±0.5mmol/L*during diet; n=9) (125). One study reported serum glucose levels during diet only (3.5-5.5mmol/L; n=2) (87) and one study reported serum glucose could not be maintained below the target of 4.4mmol/L* (n=2) (126).

2.4.4 Ongoing trials

2.4.4.1 Results of search

Seventeen records of ongoing trials were identified within study registries. After removing duplicates, 11 records relating to 11 unique trials remained (total participant n=265), all of which were eligible for this review (130–141) (see appendix D for details). Of the 11 trials, five are being conducted in the USA. All 11 studies are for adult GBM populations, with sample sizes ranging from six to 60 participants. The studies are being conducted at different time points in the treatment pathway, from new diagnosis to recurrence and are utilising different types of KDs, including energy restricted KD, intermittent fasting KD, MCT KD, MAD. Table 2.6 illustrates a summary of ongoing clinical trials.

Table 2.5: Summary of outcomes of included studies													
Population: Adult and children with gliomas													
Setting: USA and Europe													
Intervention: Any form of KD, with KD defined as a diet that is designed to produce ketones													
	Descriptors			**Critical outcomes**		**Important outcomes**							
Study	Type KD	Duration of diet	Time of commencement	Overall survival	Progression free survival	Main adverse events	Dietary retention rates	Quality of life	Acceptability	Tolerability	Compliance	Ketone levels	Glucose levels
Champ et al., 2014	✓	✓	✓	✓	✓	✓	×	×	×	✓	×	✓	✓
Nebeling et al., 1995	✓	✓	✓	✓	✓	✓	✓	×	×	×	✓	✓	✓
Rieger et al., 2014	✓	✓	✓	✓	✓	✓	✓	×	×	✓	✓	✓	✓
Schwartz et al., 2015	✓	✓	✓	×	✓	✓	✓	×	×	×	✓	✓	✓
Strowd et al., 2015	✓	✓	✓	✓	×	✓	×	×	×	×	×	×	×
Zuccoli et al., 2010	✓	✓	✓	×	✓	✓	×	×	×	×	×	✓	✓

Abbreviations: ✓= systematic review outcome present in study; ×= systematic review outcome not present in study.

Table 2.6: Summary of ongoing clinical trials						
Study	**Location**	**Population condition**	**Population size**	**Dietary intervention(s)**	**Primary outcomes**	**Secondary outcomes**
Ghodsi , 2012	Iran	Post Sx, CRT GBM	20	ER MCT KD (50% MCT, ER to 25kcal/kg/day)	Survival	Quality of life
Guimaraes Santos & Pereira da Fonseca, 2016	Brazil	Recurrent GBM	30	KD v control with intranasal administration of perillyl alcohol	Tumour size	Anthropometry
Jameson, 2014	New Zealand	Newly diagnosed GBM	20	KD (<30g CHO/day)	PFS	Ketosis Treatment compliance Dietary compliance Food satisfaction SGA Adverse events
Klein, 2014	USA	Recurrent GBM	6	ER 4:1 KD (1600kcals/day) v standard diet	Overall survival PFS Adverse events	Tolerability
Klein, 2016	USA	Newly diagnosed GBM	6	ER 4:1 KD (1600kcals/day)	Safety	Efficacy Tolerability
Rieger & Steinbach, 2012	Germany	Recurrent GBM	50	ER KD with IF (<60g CHO/day) v standard diet	PFS	Feasibility Safety Tolerability Overall survival Seizure frequency Ketosis Quality of life Depression Attention Response
Scheck, 2014	USA	Newly diagnosed GBM	14	4:1 KD reduced to MAD post CRT	Adverse events	Overall survival PFS Quality of life

Schwartz, 2012	USA	Newly diagnosed GBM	12	ER KD (20-25kcals/kg/day)	Tumour size	None stated
Song, 2016	China	Recurrent GBM	60	KD v standard diet	Adverse events	Chemotherapy sensitivity Overall survival Ketosis Quality of life
Strowd, 2014	USA	Post Sx, CRT GBM	25	MAD with IF	Feasibility	Tolerability Biological activity Glucose levels Ketosis Anthropometry Seizure frequency
Vaisman, 2010	Israel	Recurrent GBM	40	KD v standard diet	Tumour size	Performance scale Quality of life

Abbreviations: 4:1= 4g fat to 1g of carbohydrate and protein combined; CHO= carbohydrate; CRT= chemoradiotherapy; ER= energy restricted; GBM= glioblastoma; IF= intermittent fasting; kcals= kilocalories; KD= ketogenic diet; kg= kilograms; MAD= modified Atkins diet; MCT= medium chain triglyceride; MKD= modified ketogenic diet; PFS= progression free survival; SGA= subjective global assessment; Sx= surgery; UK= United Kingdom; USA = United Stated of America.

2.5 DISCUSSION

2.5.1 Summary of main results

This systematic review identified no high quality prospective studies assessing KD for glioma, but did identify a number of small RCTs that are currently on-going. All six published studies included in this review reported overall or progression free survival, however due to the limited sample sizes (ranging from one to twenty participants) and the absence of a control group, it is not possible to make any conclusions as to the efficacy of the KD interventions.

Adverse events were consistent across the majority of studies, predominately being weight loss and raised cholesterol, although two studies adopted an energy restricted KD, following which weight loss would be expected (126,128). The significance and clinical impact of weight loss would need to be considered and could be managed through non-energy restricted, non-fasting regimes supported by a trained health care professional (87). The impact of raised cholesterol profiles should also be considered within the context of the disease. Patients have a limited expected survival; therefore raised cholesterol may not be a significant patient burden and requires further investigation.

Dietary retention rates varied from 50 to 100%, but only three studies utilised a study protocol with predetermined intervention duration. As sample sizes of these studies range from two to 20 participants the external validity of such data is questionable. No study reported upon quality of life or dietary acceptability using the appropriate objective or subjective measures.

Dietary compliance was inconsistently measured, with two studies citing the presence of serum ketones as a marker of compliance (87,126), and one study using self-reported measures (125). Both methods have their limitations; including selection bias with eligibility criteria requiring patients to be compliant with the diet prior to recruitment (126) and reporter bias from self-reported measures (125). Due to the diversity in methodologies, it is not possible to determine which diet was easier for participants to comply with.

A trend for the decrease in serum glucose levels, whilst adhering to a KD, can be noted across the studies, with glucocorticoids having a negative impact on levels. However, the clinical impact of this cannot be determined from the results of the studies so far. Five studies reported upon ketones, yet due to different methodologies of urinary and serum reporting, no cross comparisons can be made between the diets.

This review also identified 11 ongoing studies, four of which were RCTs. Three RCTs may be suitable for future meta-analysis (131,132,134). These studies have comparable populations, outcome measures, control groups and similar dietary interventions, but further dietary and methodological details would be required to assess the appropriateness of such an analysis. The planned recruitment figures remain small and the trials are not powered to demonstrate efficacy. A multi-centre RCT or the ability to undertake a meta-analysis is required.

2.5.2 Overall completeness and applicability of evidence

This review identifies only six case series, with a total population of 39 adults and children with gliomas. Due to clinical and methodological heterogeneity it was not possible to conduct a meta-analysis. There was no consensus for which diet is the most appropriate in terms of efficacy, dietary retention, tolerability, compliance or adverse events. For outcomes such as tolerability and compliance, varying and in some cases inappropriate measures have been applied. No studies used validated measures to assess quality of life or dietary acceptability and are thus subject to performance bias. The effect of a KD on these outcomes is unknown. Whilst studies note the KD to reduce serum glucose and increase ketones, desired targets have not been established through this review. The evidence base has also yet to establish a favourable point in the treatment pathway at which the diet should commence and for what duration. Thus, demonstrating the limitations of evidence for KD in gliomas and resulting in a lack of meaningful conclusions. Any observations noted in improved survival times could be a mere coincidence, highlighting the need for further, high quality research to address these issues.

2.5.3 Quality of the evidence

The quality of the evidence is very low due to small sample sizes and high risk of bias, secondary to the methodological limitations of the case series. Heterogeneity existed across the studies, due to differences in methodologies, dietary interventions and commencement of diet in relation to the treatment pathway. Further research is required, providing high quality evidence in which clinical guidelines and services could be directed.

2.5.4 Potential biases in the review process

Databases were thoroughly searched to identify studies suitable for this review. Application of the eligibility criteria to the results identified six studies for inclusion. Given the relative novelty of KD in its application to gliomas, a low number of editorials were expected. As the search strategy was first piloted and the results of the search strategy supplemented by hand searches, it is unlikely that relevant studies were missed, further confirmed through contact with an expert in the field. Therefore conclusions drawn from the review are based upon all available evidence.

Language bias is present in this review. Included studies were limited to those published in the English language, which may influence the positive nature of the findings. Publication bias is difficult to omit, yet through searching study registries, including grey literature and contacting experts in the field, the review has minimised this element.

A key strength of this review lies in the quality assessment of included studies. The Institute of Health Economics (IHE) (Canada) Case Series Quality Appraisal Checklist (111) is the only validated quality appraisal tool for assessing the methodological quality of case series.

A key strength of the IHE Case Series Quality Appraisal Checklist lies within its methodological development; a Delphi process to devise the appraisal tool criteria, a pilot exercise assessing inter-rater reliability, and a formal validation process using principle component analysis (111,142). The tool is specifically designed for use in treatment intervention case series studies. The tool was also updated to include assessor annotations specific to this review as recommended by the tools authors (111), to aid the quality appraisal process (see appendix B). The tool does not provide a scoring system in which study quality may be distinguished as high or low, hence it was not possible to strictly assess the confidence of cumulative evidence. As such, a narrative approach was taken in this review. No study fulfilled the full study-design criteria of the quality assessment tool. Further validation of the IHE Case Series Quality Appraisal Checklist is ongoing.

Three studies utilised, and were contacted to provide, a study protocol (87,125,126). One study author (126) provided the trial protocol and there appeared to be no suggestion of selective reporting bias. Despite Nebeling et al. (1995) (87) utilising a study protocol, study eligibility criteria were not commented upon in the publication, creating low internal validity. Protocols were not used in the remaining studies (124,127,128), therefore there is an unclear risk of reporting bias for these studies as the information provided in study publications is

the limit to knowledge of the methodologies used and outcomes reported. Quality assessment in these cases could not adequately be addressed, resulting in unclear risk of bias judgements. It is also unclear if any studies blinded assessors to the intervention that participants were receiving; consequently it was not possible to assess performance or detection bias in any study.

One study included a retrospective control group (124), but failed to statistically or descriptively compare the control group to the dietary intervention group. The control group was also unlikely to represent the population due to convenience sampling methods and eligibility criteria requiring variables not held within the records, thus creating selection bias. Therefore this study design was also considered a case series.

A meta-analysis was not undertaken in this review for several reasons. Study populations varied from newly diagnosed grade III or IV gliomas to recurrent gliomas, thus receiving varying oncological treatments whilst receiving the dietary intervention. The dietary interventions also varied, in terms of energy restrictions, carbohydrate restrictions and types of dietary fats included. One trial also included fermented yoghurts and plant oils in addition to KD, presenting difficulties in evaluating clinical benefits. Outcomes were variable between studies, along with the methodologies used to assess these outcomes and it was not possible to establish treatment effects as trials were underpowered. Therefore a meta-analysis was not undertaken as the overall measure of treatment effect would be misleading. Ongoing studies may provide appropriate data and synergy between protocols to allow for meta-analysis in future reviews.

2.5.5 Agreements and disagreements with other studies and reviews

We found no convincing evidence for the efficacy of KDs in gliomas and it is not possible to distinguish if one KD diet holds promise over another KD. Dietary acceptability within this population also remains to be established. The current evidence suggests that KDs do not appear to be harmful to this population. Hence, this review is in agreement with the current standard of care for glioma patients and is in keeping with previous literature.

2.6 IMPLICATIONS

2.6.1 Implications for practice

Due to the lack of high quality evidence it is difficult to justify the use of KDs in a clinical, non-research setting. Further evidence is required to explore efficacy, dietary acceptability and an assessment of cost effectiveness, prior to its implementation alongside the current standard of care in this population. There is no evidence to justify the use of KDs as a replacement for the current standard of care.

2.6.2 Implications for research

Key areas for future research are:

1. A pragmatic feasibility study to inform future RCT design; with outcomes related to adverse events, dietary retention rates, quality of life, dietary acceptability, tolerability and compliance, using validated measures.
2. Determining if KDs are effective in the management of glioma, through high quality RCTs. It will be important to consider which KD, if any, is beneficial and at what point in the treatment pathway. KD concurrent to chemoradiotherapy in animal models has proven to potentiate the treatment effects; however, this is yet to be replicated within patients with GBM.
3. A health economic assessment to establish efficiency, clinical effectiveness and value of the intervention, would be beneficial. Establishing quality adjusted life years would be of benefit to assess disease burden, in terms of quality and quantity of life gained by patients, if at all any.

2.7 CONCLUSION

This review is based on case series evidence, the lowest position in the evidence hierarchy. At present this is the only published evidence available to inform decisions regarding the

implementation of KDs for gliomas. While the review has found minimal adverse events, suggesting KDs to be safe in this population, the evidence for efficacy and acceptability of various KDs is insufficient to suggest they have a therapeutic effect in the management of gliomas. Further high quality research would be of benefit.

2.8 ACKNOWLEDGEMENTS

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CHAPTER 3

ESTABLISHING A NHS KETOGENIC DIET SERVICE AND AN ASSESSMENT OF THE LEVEL OF PATIENT INTEREST FOR KETOGENIC DIETS IN GLIOMA

3.1 CHAPTER OVERVIEW

Before a ketogenic diet (KD) clinical trial could be established, it was important to assess patient demand for KD in glioma and if a KD service could be delivered within the National Health Service (NHS). At this stage, the only funded KD services within the NHS were for paediatric patients with epilepsy; therefore no infrastructure was in place to support a KD clinical trial for adult patients with glioblastoma (GBM).

This chapter begins by discussing the potential benefits of involving patients in research, before considering the challenges of establishing a trial to assess the efficacy of KD interventions for patients with gliomas within the NHS. A survey and scoping service were utilised to explore these issues, the methodology for which is explained. The chapter then presents the survey and scoping service results, before discussing the results and limitations to the study design, concluding with recommendations for future trials.

3.2 INTRODUCTION

When establishing a trial to explore the clinical effectiveness of a novel intervention, it is unrealistic to envisage embarking on a randomised controlled trial (RCT) without any fundamental foundations. First, it is important to understand if patients would be interested in participating in the trial, if they consider the intervention to be agreeable and if the research area is of interest to them, in order to explore the demand for services and scope for recruiting to clinical trials (143,144). When relating this to a KD trial it is important to consider; i) if there is sufficient local and national interest in KDs within the glioma community; ii) if a KD service is offered to patients with glioma, which patients will follow the diet and at what point in the patient pathway; and iii) if KD can be delivered to adults in an NHS setting.

Secondly, assessing the efficacy of interventions such as KDs within the NHS poses a number of challenges that need to be considered in order to inform trial design and feasibility. One challenge being the lack of commissioned KD services in adult care settings, in which to support a multi-centre RCT. However, without good evidence of clinical and cost effectiveness a KD service would not be commissioned. Therefore, it was important to consider if a KD service could be established in a centre with no prior experience, for the purpose of supporting recruitment to a clinical trial. This experience would provide an essential learning experience if a trial were to be used as a means to develop new KD services in recruiting sites.

Another challenge was selecting the most appropriate KD to inform trial design. When developing the initial scoping service and survey, the following KDs were considered:

- Classical ketogenic diet (CKD)
- Energy restricted ketogenic diet (ERKD)
- Modified ketogenic diet (MKD)
- Modified Atkins diet (MAD)

The relative strengths and weaknesses of these diets are discussed in table 3.1.

MKD was chosen above CKD, ERKD and MAD[3] to assess initial interest as it is the least restrictive KD. At this time, MKD was also offered to a limited number of adults with epilepsy

[3] Little was known about the use of MCT KD in neuro-oncology when the initial scoping service was set up in 2015; therefore this KD was not considered.

in the UK private healthcare sector, hence a basic understanding of palatability was known (145). Yet, as MKD lacked the strict implementation of other KDs, a protocol was implemented to ensure standardisation of procedures and comparability, whilst still allowing a degree of flexibility to suit individual requirements, given this is a dietary intervention.

3.2.1 Aim and objectives

Aim:

- To explore KD service deliverability for patients with gliomas and assess patient interest.

Objectives:

- To assess if there is sufficient local and national interest from patients with gliomas to support a KD RCT.
- To evaluate if MKD could be delivered to adult patients with gliomas in an NHS setting.
- To explore the characteristics of patients who follow MKD and at which point in their treatment pathway.

Table 3.1: Summary of the strengths and weaknesses for the use of different KDs in GBM		
Diet	**Strengths**	**Weaknesses**
CKD	• Used in paediatric drug-resistant epilepsy since 1920s. • Animal models demonstrate efficacy (77). • Produces higher ketone levels due to fat: carbohydrate ratio with higher ketone: glucose ratio showing to have greater benefits in animal models (146).	• Animal models utilise unrealistic dietary ratio for people (e.g. 6:1), resulting in low palatability. • Lacks sufficient protein to meet adult nutritional requirements, in healthy and oncological states (147,148). • Requires strict implementation; dietary items to be weighed and calculated using computer assisted programmes. • Requires the use of ketogenic nutritional products resulting in additional costs to the NHS as only available via prescription. • Deficient in micronutrients (149).
ERKD	• Reduces angiogenesis, oedema and tumour growth in animal models (150,151). • Energy restriction promotes ketone production.	• Does not meet nutritional requirements resulting in weight loss (126,128). • Low palatability. • Requires strict implementation; dietary items to be weighed.
MAD	• Designed for ease of use and to aid compliance, no requirement to weigh food items (152). • Notably less side effects than CKD and MCT KD (53). • Implementation protocol in situ from John Hopkins Institute. • No need for a fasted start or hospitalisation prior to dietary commencement (153).	• MAD permits protein to 25% of ETER, therefore patients consume double their usual protein intake (on average) which in turn could promote the secretion of glucagon and insulin (154), thus limiting the ketotic state. • Requires the use of ketogenic nutritional products at implementation resulting in additional costs to the NHS as only available via prescription.
MKD	• Designed for ease of use and for aiding compliance. • Used in UK clinical practice for treatment drug-resistant epilepsy in adults and paediatrics (55). • Allows for flexibility in implementation and education compared to John Hopkins MAD protocol (55,145,155). • Can be nutritionally complete when implemented with a dietitian (149). • Fewer side effects than other, high fat, KDs (53). • Does not require ketogenic nutritional products. • Offers adequate protein for use in adult oncology (147,148).	• Umbrella term for 'modified' KDs that do not exclusively follow John Hopkins protocol, resulting in variation in implementation strategies and macronutrient content. • Requires some skill with weighing/ quantifying portion sizes.

3.3 METHODOLOGY

3.3.1 Patient survey

Surveys are commonly used to seek explanation or understanding of a topic and to provide data for hypothesis testing (156); in this case to explore if patients with gliomas would be willing to participate in a KD RCT. A cross-sectional patient survey was designed by a multi-disciplinary team, including a neurosurgeon, neurologist, biostatistician and dietitian at the University of Liverpool and The Walton Centre NHS Foundation Trust (WCFT), with expertise in the area of neuro-oncology and/or clinical trial design.

All surveys included a covering letter to assist patients with providing informed responses (156). The covering letter included a brief summary of the literature regarding KDs and their use in glioma management, foods permitted and excluded from the MKD, anticipated dietary duration, potential risks associated with the diet and potential monitoring required by the patient and clinician. Contact details for the study team were also provided should the patients have any further questions. By completing the survey, consent to participate was assumed.

The survey explored patients' baseline demographics, attitudes towards the use of the MKD for glioma, their willingness to try the diet and willingness to participate in a future RCT. Questions were grouped by topic for ease of reading (see appendix E).

The survey was piloted by patients at WCFT, to ensure the wording, order of questions and covering letters were appropriate before being distributed nationally (see appendix F). The survey contained closed questions, therefore the pilot ensured sufficient and appropriate response categories were available. Following the pilot, minor alterations were made to the wording of the covering letter and three further questions were included; tumour type, prior knowledge of KD and dietary changes since diagnosis. Questions relating to veganism, ready meal use and supermarket preferences were removed after offering little value in the pilot.

Non-random, convenience sampling methods were used to recruit patients (156). All patients attending WCFT neuro-oncology clinics between August 2015 and January 2016 were invited to complete the WCFT survey. Patients were approached to participate by their treating neurosurgeon or oncology nurse. The national survey was distributed online via brain tumour charity websites and their social media outlets between January 2016 and March 2016 (Matthew's Friends, Astro Brain Tumour Fund, The Brain Tumour Charity, brainstrust). Patients who completed this survey opted-in with regards to completion.

Descriptive analysis of the results was undertaken and no power calculation was required for the survey (156). However, it is appreciated that larger samples provide a better estimate of the population.

3.3.2 NHS KD scoping service

Patients attending neuro-oncology clinics at WCFT were also offered the opportunity to try the MKD for a three month period, with the aim of evaluating if a KD service could be established within the NHS for patients with gliomas. Patients were referred to the dietitian via their neurosurgeon, neuro-oncologist or oncology nurse (providing the consultant's permission was sought). Patients could commence the diet at any stage during their treatment pathway. All patients considered for the service were required to meet the following eligibility criteria.

Inclusion criteria:

- Aged ≥16 years
- Patient at WCFT
- Performance status ≤2 (157)[4]
- Confirmed histological diagnosis of high grade glioma
- Undergone surgical resection of tumour

Exclusion criteria[5]:

- Any prior use of a KD
- Kidney dysfunction (Chronic Kidney Disease III/IV, renal stones, cancer, low phosphate/potassium/salt diets)
- Liver dysfunction (alcoholic liver disease, non-alcoholic liver disease, cancer, hepatitis, haemochromatosis, primary biliary cirrhosis)
- Gall bladder dysfunction (gallstones, cholecystectomy in past 12 months, cancer)

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[4] Performance status (PS) 0 is defined as normal activity; PS 1 is defined as some symptoms but nearly fully ambulant; PS 2 is defined as less than 50% daytime in bed; PS 3 is defined as great than 50% daytime in bed; PS 4 is completely bed bound (157).

[5] To minimise participant bias, patients with prior use of KDs were excluded. Diabetes, kidney, liver, gall bladder, metabolic and eating disorders are contraindications for the diet as recommended by the International Ketogenic Diet Study Group (293). Weight loss medications such as orlistat are contraindicated in KDs due to the limitation in the absorption of fat, which could result in gastrointestinal issues. Underweight patients, defined as BMI less than 18.5kg/m^2, were excluded due to the risk of malnutrition and the possibility that nutrition support may be indicated (294).

- Metabolic disorder (carnitine deficiencies, β oxidation defects [medium chain acyl-CoA dehydrogenase deficiency, very long chain acyl-CoA dehydrogenase deficiency, short chain acyl-CoA dehydrogenase deficiency, long chain 3-hydroxyacyl CoA deficiency, medium chain 3-hydroxyacyl CoA deficiency], pyruvate carboxylase deficiency, porphyria)
- Eating disorder (anorexia nervosa, bulimia nervosa, binge eating disorder)
- Diabetes (requiring medication)
- Body mass index (BMI) ≤18.5kg/m^2
- Current use of weight loss medications (Orlistat, Belviq, Contrave, Saxenda, Phentermine, Qsymia)
- Performance status ≥3 (157)

3.3.2.1 Baseline assessment

Patients were contacted by telephone to discuss their referral and the MKD. An appointment was then provided with the dietitian to discuss MKD in further detail. Literature explaining the diet and the scoping service was posted to the patient. Prior to commencing the MKD, baseline assessments were undertaken by the dietitian; including anthropometric measures (weight, height, BMI, mid arm muscle circumference, fat mass), biochemistry monitoring (renal, bone, liver function test (LFT), fasting lipid, fasting glucose, carnitine) and review of a three day habitual food diary were recorded.

3.3.2.2 Dietary commencement

Once biochemistry was returned within range, patients were able to commence the diet. The macronutrient content of MKD was 70% fat, 20g carbohydrate and protein ad lib (55).

Patients received dietary education and literature regarding MKD, recipes, ketostix® urine test strips (Bayer, Leverkusen, Germany), ketone diaries and a personalised seven day MKD diet plan calculated by the dietitian, when commencing the diet.

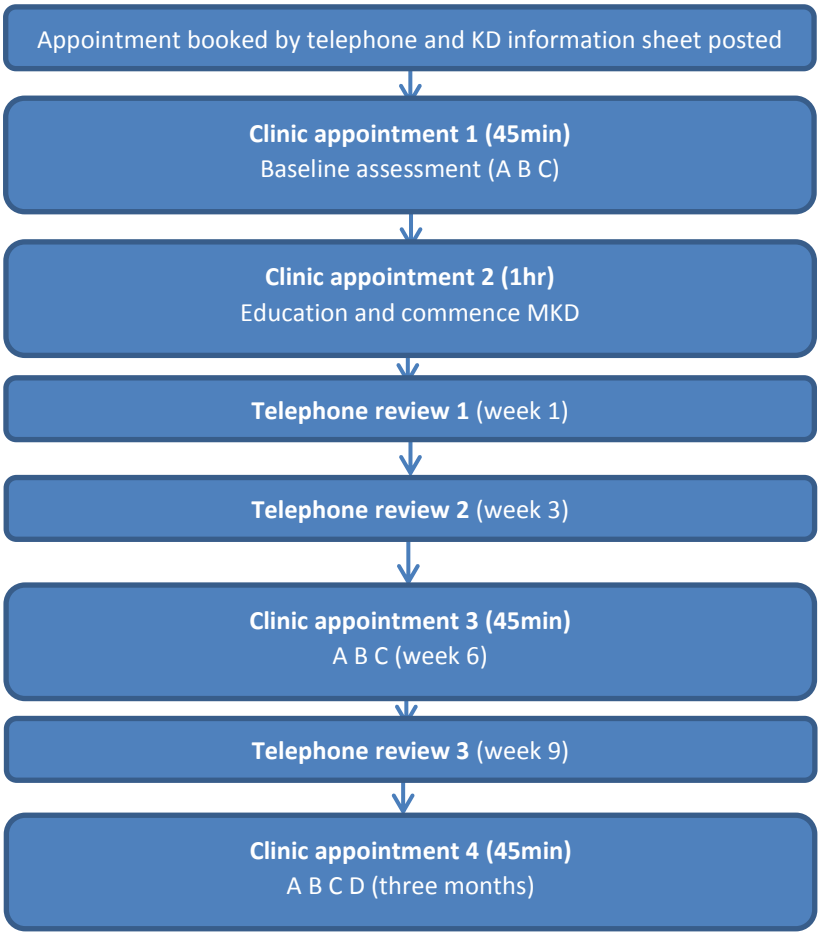
Patients were instructed to check their urinary ketones twice daily for the first month, once per day for the second month, then twice weekly in the third month of diet and record these figures in the ketone diary provided. Adequate urinary ketosis was defined as values ≥4mmol/L (152).

3.3.2.3 Dietetic follow up

After commencing the diet, patients were assessed by the dietitian in clinic at six weeks and three months, and by telephone review at weeks one, three and nine. During clinic assessments anthropometry, biochemistry and food and ketone diaries were collected and

reviewed. Telephone reviews were utilised for trouble-shooting and on-going dietary support. Dietary advice was tailored to the patient's individual requirements. Figure 3.1 provides a schematic of the service design and the timing and type of assessments undertaken.

Figure 3.1: Schematic of scoping service



Key	
A	Anthropometry (weight, height, BMI, MAC, TSF, MAMC, FM)
B	Biochemistry (renal, bone, LFT, fasting lipid, fasting glucose, carnitine [only on initial screen])
C	Collect food and ketone diaries
D	Exit survey

Abbreviations: BMI = Body Mass Index; FM = Fat Mass; LFT = Liver Function Test; MAC = Mid Arm Circumference; MAMC = Mid Arm Muscle Circumference; TSF = Triceps Skin Fold.

Nutritional analysis of food diaries was undertaken using DietPlan 7© (Forestfield Software LTD, Horsham, UK). Dietary compliance and tolerance were monitored, along with changes to medications; however, medications were permitted to be altered in-line with the clinician's recommendations. Radiotherapy and chemotherapy were provided in-line with the current standard of care.

For those patients who wished to continue with the MKD after the initial three month period, follow up with the dietitian was offered quarterly in clinic, with anthropometric measures, biochemistry and food and ketone diaries being collected.

One full time equivalent dietitian employed by the WCFT was supplied through an NIHR research capacity grant. The dietitian was collaborating on both this study and one other study. The service was dietetic led, with the dietitian reporting any medical concerns directly to the consultant neurosurgeon. Time logs were held by the dietitian to help inform future service provision and research capacity.

3.3.2.4 Exit survey

Patients completed an exit survey to assess dietary tolerance, willingness to participate in future trials and to evaluate the dietetic service after following MKD for three months or at the point of diet discontinuation if prior to this (see appendix G). Patients received the survey by post or in person in the clinic.

3.3.2.5 Analysis

Descriptive statistics were used to summarise the results of the patient survey data and the NHS KD scoping service. The study was not powered to measure efficacy.

A 12 week cost analysis was calculated from the time logs completed by the dietitian, in addition to biochemistry monitoring (standard laboratory pricing) and ketostix use (ketostix costs calculated based on cost per unit). Clinical time was associated with patient facing activities in clinics. Non-clinical time was associated with non-patient facing activities (e.g. analysing food diaries, calculating meal plans). Administrative tasks (e.g. letter drafting) was completed by an administrator. Costs were then calculated based on the median number of dietetic and admin hours per patient, based upon the midpoint of NHS staff Agenda for Change banding. This was supplied by the WCFT finance team.

3.3.2.6 Ethical approval

The scoping service was approved by WCFT Research, Development and Innovation committee. All patient literature, including surveys, were approved by WCFT Patient Information Group.

3.4 RESULTS

3.4.1 Patient survey

172 surveys were completed; 50 at WCFT and 122 nationally. The responses from the pilot survey at WCFT and the national survey are presented separately.

3.4.1.1 Baseline demographics

WCFT pilot survey:

Sixty eight percent (n=26) of participants were male, 32% (n=12) female, 24% (n=12) not recorded, all aged between 30 and 69 years.

National online survey:

Thirty six percent (n=43) of participants were male, 64% (n=76) female, 3% (n=3) not recorded. All were aged between 16-69 years. Diagnoses were self-reported by the online population group; 30% (n=35) GBM (grade IV), 25% (n=30) anaplastic astrocytoma or oligodendroglioma (grade III), 43% (n=50) low grade glioma (grade II astrocytoma or oligodendroglioma and 2% (n=2) other. Fifty eight percent (n=70) of the online population reported prior knowledge of KD, with charity websites (n=38, 39%) and online forums (n=22, 22%) being key information sources. Since receiving their diagnosis 55% (n=65) had made changes to their diet.

3.4.1.2 Willingness to participate in a clinical trial

WCFT pilot survey:

Fifty six percent of patients (n=29) would be willing to participate in a clinical trial to investigate deliverability and tolerability of the diet. Of these, 46% (n=17) would still be willing to participate in the trial if it were randomised between MKD with standard care and standard care alone. Sixty five percent (n=31) of patients would be willing to try MKD for three months. Forty eight percent (n=15) would prefer to commence the diet before surgery, 23% (n=7) immediately after surgery, 13% (n=4) after surgery during chemo-radiotherapy and 16% (n=5) after radiotherapy during chemotherapy.

National online survey:

Seventy one percent of patients (n=85) would be willing to participate in a clinical trial to investigate effectiveness and tolerability of the diet. Of these, 61% (n=45) would still be willing to participate in the trial if it were randomised between MKD with standard care and

standard care alone. Seventy eight percent (n=94) of patients would be willing to try MKD for three months. There was no clear preference in timing of when to start the diet: 20% (n=33) preferred to start the diet before surgery, 22% (n=35) immediately after surgery, 15% (n=24) after surgery during chemo-radiotherapy, 11% (n=17) after radiotherapy during chemotherapy and 32%, (n=52) after treatment during the monitoring phase. Patients were also questioned about their motivators and barriers to participating in a clinical trial (table 3.2 and 3.3).

Table 3.2: Motivating factors to trial participation		
Motivating factors	**WCFT number of responders n (%)**	**National number of responders n (%)**
To help other adults with glioma	30 (31)	90 (37)
To access the diet myself	23 (23)	66 (27)
To get expert advice about the diet	20 (20)	65 (27)
To improve quality of life	25 (26)	0 (0)
Other	0 (0)	18 (7)

Table 3.3: Barriers to trial participation		
Barriers to participation	**WCFT number of responders n (%)**	**National number of responders n (%)**
Extra expense of travelling	6 (14)	46 (24)
Extra burden on visiting a dietitian	12 (28)	27 (14)
Extra expense of the diet	8 (18)	31 (16)
Fear of side effects	0 (0)	25 (13)
Not applicable (no perceived burden)	0 (0)	24 (13)
Not enough time to devote to the study	6 (14)	10 (5)
Carer or family burden	0 (0)	11 (6)
Do not wish to participate in a study	2 (5)	2 (1)
Other	9 (21)	16 (8)

3.4.1.3 Ketogenic service demand

WCFT pilot survey:

Fifty seven percent (n=28) of the WCFT population reported patients with gliomas should have access to the MKD.

National online survey:

Seventy six percent (n=91) of the online population reported patients with gliomas should have access to the MKD.

3.4.2 NHS KD scoping service

Eight adults with high grade glioma (n=7 glioblastoma [WHO grade IV]; n=1 anaplastic astrocytoma [WHO grade III]) were referred for consideration of MKD. Six patients commenced diet (n=5 GBM; n=1 anaplastic astrocytoma), whilst two patients declined the dietary intervention due to their deteriorating performance status. There were no contraindications to MKD in any patient. Table 3.4 illustrates baseline patient demographics of the six patients who commenced MKD.

Table 3.4: Baseline demographics

Patient	Gender	Age	Histological diagnosis[ł]	Treatment during KD	Prior treatment	Dexamethasone dose (mg/d) during diet
1	Male	34	Glioblastoma; *IDH*-wildtype	CCNU	Sx, RT, TMZ	0-1[*]
2	Male	47	Glioblastoma; *IDH*-wildtype	RT, TMZ	Sx	2-6[*]
3	Male	66	Anaplastic astrocytoma; *IDH*-wildtype	RT, TMZ	Sx	0
4	Male	44	Glioblastoma; *IDH*-mutant	TMZ	Sx, RT, Sx, Glial wafers	0-12[ł]
5	Male	45	Glioblastoma; *IDH*-wildtype	TMZ	Sx, RT	0.5-1[*]
6	Male	49	Glioblastoma; *IDH*-wildtype	RT, TMZ	Sx	2

Abbreviations: Bx= biopsy; CCNU =Lomustine; IDH = Isocitrate dehydrogenase; KD = Ketogenic diet; RT = Radiotherapy; TMZ = Temozolomide; Sx = Surgical resection. Legend: ł Histology classified by WHO 2007 criteria in use at time of diagnosis (158). *Dexamethasone dose decreased whilst on diet. ł Dexamethasone dose increased whilst on diet.

3.4.2.1 Attrition

Of the six patients who commenced MKD, four completed the three month intervention period. Two patients discontinued the diet before three months, one (anaplastic astrocytoma) due to clinical deterioration leading to hospital admission, where the MKD was unsustainable, and one patient (GBM) due to dietary preferences. Median dietary duration for those discontinuing diet was 34 days (range: 22-45 days). One patient temporarily discontinued the MKD for three weeks during the intervention period due to an unrelated chest infection, following which the diet was reinstated. Of the four patients who completed the three month intervention period, three stayed on the diet for the longer term (≥360 days), whilst one discontinued the diet after 167 days due to tumour progression and clinical deterioration.

3.4.2.2 Dietary tolerance

Two patients reported constipation whilst following MKD. Constipation was reported in the first two weeks after commencing the diet and resolved with dietary modification in all patients. No other dietary intolerances were reported by patients, such as diarrhoea, nausea, vomiting or acid reflux.

3.4.2.3 Ketosis

Adequate urinary ketosis of ≥4mmol/L was achieved in all patients within one week of commencing the diet. Of those who completed three months of diet (n=4), three maintained ketosis during this time. The patient who temporarily discontinued the MKD for three weeks due to a chest infection did not maintain ketosis during this time.

3.4.2.4 Anthropometry

Table 3.5 illustrates anthropometry (body composition) at baseline and at follow up, after completing 12 weeks of MKD (n=4). No clinically significant changes were noted between measures pre and post diet.

Table 3.5 Anthropometric changes over 12 weeks

Measure	Baseline	3 month review
Weight (kg)	85.6 (11.7)	84.6 (9.6)
BMI (kg/m2)	25.2 (23-29.6)	25.1 (23.4-28.4)
Mid arm muscle circumference (cm)	25.9 (22.1-32)	30.2 (26.7-31)
Fat mass (%)	22.0 (11.2-25.6)	23.0 (12.2-23.9)

Paired values were available for n=4 for all measurements. Values are median (range) except weight illustrated as mean (standard deviation).

3.4.2.5 Laboratory values

Changes in laboratory values are illustrated in table 3.6 for patients with baseline and 12 week follow up data (n=4). No derangements were noted in renal, bone or liver function biochemistry results.

Table 3.6: Laboratory values		
Measure	**Baseline**	**3 month review**
Total cholesterol	5 (3.6-6.2)	7.4 (4.4-8.3)
LDL	2.9 (2.1-4)	4.7 (2.3-6.2)
HDL	1.8 (0.8-2.2)	1.4 (1.4-2.6)
TG	0.94 (0.5-2.9)	1.3 (0.9-1.6)
Cholesterol : HDL	3 (3-5)	3.8 (3.1-5.9)

Paired values were available for n=4 for all measurements. Values are median (range). Abbreviations: LDL = Low Density Lipoprotein; HDL = High Density Lipoprotein; TG = Triglycerides.

3.4.2.6 Exit survey

Six patients completed an exit survey to assess their experience of the diet and service provided. Five patients reported their weekly grocery shop had increased in cost since commencing MKD, mainly due to the added expense of high protein foods, such as meat and fish, fats such as olive oil and specialist carbohydrate free food products. However, the financial costs to patients were not specified.

All patients would recommend the MKD and all patients would recommend the WCFT ketogenic service to other patients. The majority of patients (n=4) would recommend commencing the diet after surgery, before radiotherapy, from their experiences. Four patients expressed an interest in participating in a clinic trial to assess effectiveness and tolerability, of which one patient would still be interested if the trial were randomised into MKD with standard care and standard care alone (i.e. no dietary change). All patients would consider following the diet for longer than three months as part of a clinical trial.

3.4.2.7 Cost analysis

Costs of the initial 12 week intervention can be found in table 3.7. These costs were based on the dietetic intervention equating to 8.8 hours per patient (4 non clinical, 4.8 clinical) over a 12 week period. Biochemistry and ketone monitoring were calculated based on timings and tests stated in methodology above.

Table 3.7: Cost analysis	
Item	**Cost per patient for 12 weeks (£)**
Dietitian (mid-point band 6 salary)	148.50*
Biochemistry monitoring	108.69×
Urinary ketone monitoring	11.20
Administration support	17.61#
Total	286.00

*Dietetic intervention equated to 8.8 hours per patient (4 non clinical, 4.8 clinical) over a 12-week period. × Carnitine accounts for £52.26 of total biochemistry costs. All costings are based on patients who completed the full 12 weeks (n=4). #Administration support equated to 2 hours per patient over a 12 week period.

3.5 DISCUSSION

The results of this study show MKD to be deliverable within a NHS setting in a centre with no prior experience of KDs; essential information when considering the infrastructure required to support a multi-centre RCT. Survey data indicates that there would also be sufficient patient interest to support a national multi-centre trial. Patient participation in a clinical trial would be affected by randomisation if the control arm was standard treatment with no KD. The findings related to patient interest in KD aligns with the James Lind Alliance Neuro-Oncology Priority Setting Partnership report that identified the influence of lifestyle factors (including diet) on tumour growth to be one of the top 10 clinical uncertainties (1). Since the most effective way to assess dietary influence and therefore effectiveness would be to undertake a RCT, careful consideration of the trial design would be needed to ensure maximum recruitment, whilst achieving maximum methodological integrity. Nevertheless, the patient survey results should be interpreted with caution due to reporting bias, especially results generated from the online population, since those interested in KDs may be more likely to seek out information online and via charities, which has led to a positive bias in the survey data when comparing online and WCFT populations.

The key motivators for participation in KD clinical trials were distributed between altruism (helping others), improving quality of life, having personal access to the diet and gaining expert advice, which should be considered in future trial designs or service models. The main barriers to participating in a KD trial include burden of dietetic visits and extra expense of travel. Burden of dietetic consultations can be addressed using the proposed service design since telephone consultations negate the expense of travel, the inconvenience of clinic attendance and require less dietetic time. Dietitians should consider cost implications when devising diets, since the patients reported an increase in the weekly grocery shop whilst on diet. This could be addressed by the prescription of ketogenic dietary supplements, although

this would increase the cost burden to the NHS; an aspect worthy of further investigation using health economic frameworks (159).

Of the eight patients referred into the service, six were started on diet. Two patients, one a newly diagnosed GBM post resection, the other a recurrent GBM receiving second line chemotherapy, were not able to attend the first clinic appointment due to rapid disease progression and clinical deterioration resulting in a poor performance status. This highlights the challenges of starting the diet in a timely manner and it would be beneficial for future service designs and clinical trials to consider performance status as part of the eligibility criteria. The WCFT has a catchment population of approximately 3.5 million and treats around 100 to 120 patients with newly diagnosed glioblastoma each year. After setting up the KD service it received one referral per month which represents only 10% of all new GBM patients. The low referral rate is likely to be due to a combination of factors, including a lack of awareness by referring clinicians, as well as a lack of suitable patients. The expected referral rates and patient demand should be considered when designing trials and determining the number of trial sites.

In the clinic, four patients completed the initial three months of diet and the attrition rates are comparable to those seen in previous studies (125,127). However, it is important to note the higher carbohydrate intake of 60g/day in the ERGO study (125), which is likely to improve dietary tolerance and compliance. Of those who completed the initial three months (n=4), three stayed on the diet for the longer term, which highlights the tolerability of the diet and the motivation of the patients in the scoping service who self-selected to try MKD whilst undergoing treatment for a terminal tumour.

Side effects were limited, with only two patients reporting constipation which was resolved through dietary changes (the inclusion of daily linseeds/flaxseeds and increased oral fluids). No other side effects were reported by patients, including diarrhoea, nausea, vomiting or acid reflux, comparing favourably to a previous study of KD in cancer patients (125) and was below that reported in MKD epilepsy populations (152,160–162). Whether this is as a result of reporter bias or perhaps due to patient perception of acceptable gastrointestinal side effects requires further investigation. There were no clinically relevant changes in cholesterol profiles (cholesterol ratio maintained below 4) over the course of the diet, contradicting previous literature (152,163). Longitudinal data, of larger populations, may provide a more informative result. The lack of reported side effects in this limited number of patients, provides some reassurance that the diet is safe in the glioma population. In

addition, there was a median increase of 5.4cm in mid arm muscle circumference over three months, which suggests that the MKD may not be detrimental to the nutritional status of glioma patients. This is further supported by the minimal change to weight, BMI and fat mass, over the three month period. The increase in muscle could be as a result of the athletic and gender bias of our population, rather than simply diet, with six participating in weight bearing exercise, five of who maintained a daily aerobic exercise regime. Future studies are required to investigate this effect in a larger population.

Adequate urinary ketosis is deemed to be ≥4mmol/L (152), and was achieved in all patients. Stable ketosis was achieved in three patients who completed the three month dietary period. Urinary ketones were the measurement of choice, due to cost implications associated with blood ketone monitoring (£0.09 per urinary ketone strip versus £2.50 per blood ketone strip). This is acknowledged as a potential methodological limitation due to effects of hydration and time lag on readings, however laboratory or home testing would have been prohibited due to cost for implementation in this service. Urinary ketones are also limited to measuring acetoacetate and changes in the ratio of acetoacetate to beta-hydroxybutyrate, may result in low readings, as the patient becomes keto-adapted. In future trials, blood ketones may be considered, but the implications of monitoring should be considered within NHS economic models and frameworks.

Dietetic involvement per patient over three months was 8.5 hours (4 hours non clinical, 4.8 hours clinical), costing £286 per patient for 12 weeks. In previous KD trials in paediatric epilepsy [15, 17] and for commissioned paediatric epilepsy KD services patients are screened for carnitine deficiencies and fatty acid oxidation defects. We also undertook carnitine testing in our pilot, but all tests were negative. Given that fatty acid disorders are rare in adults [26] and the MKD allowing free protein (source of carnitine) carnitine testing would arguable not be necessary in future adult glioma trials or KD services. Health economics, perhaps utilising quality adjusted life years (QALYS), would be beneficial if a large scale RCT were undertaken (159). These patients were following the diet at various stages of treatment (table 3.4) which provides information on how the diet is tolerated during all parts of the patient pathway. The two patients who discontinued diet before three months were following a MKD whilst receiving adjuvant chemo radiotherapy. Whilst the literature from animal models cites this to be the most opportune time in relation to efficacy (164,165), patients are more likely to suffer from side effects of the treatments at this point, including fatigue and nausea. Despite this, four of the patients who completed an exit survey would

recommend consuming a MKD whilst receiving adjuvant chemo radiotherapy. Future trials should assess the tolerability of MKD at this time-point.

The study had several limitations. In relation to the survey, non-random, convenience sampling was used at WCFT and patients self-selected to complete the online national survey, both of which could create a positive bias in the results. Following the WCFT pilot, tumour demographic information was incorporated into the national survey, consequently this information is lacking in the 50 WCFT responses.

In relation to the scoping service, the small numbers of patients included were self-selecting, self-referring patients, who all started MKD at different time-points in their treatment pathway. This limits the generalisability of our results in the context of the high grade glioma population as a whole. The number of patients with whom KD was discussed remains unknown; therefore it is difficult to determine if adequate recruitment could be achieved in a clinical trial setting. Despite the high levels of patient interest illustrated in the previous surveys, this interest may not directly translate into adequate recruitment and patients' willingness to take part. Importantly, this study shows that the MKD can be delivered within the NHS setting. Since the study was not designed to assess efficacy, the impact of MKD on tumour control could not be assessed, and whilst all patients self-reported good quality of life, this was similarly not objectively assessed.

3.6 IMPLICATIONS

3.6.1 Implications for practice

- Ketogenic services for patients with gliomas can be established within a dietetic-led NHS setting, should new services be required to support a multi-centre RCT.
- From the small patient sample, MKD appears to be safe for use within this population, as an adjuvant to standard treatment at various points in the treatment pathway.
- Further research to establish the efficacy of KDs in gliomas is required before KDs can be offered in mainstream healthcare; KDs are currently not supported by NICE guidelines (166).

3.6.2 Implications for research

- There is interest from the glioma patient community to support clinical trials with KD interventions. Randomisation to a control arm of 'no diet' could affect recruitment. Further patient and public involvement (PPI) would be critical to ensure study methods are acceptable to patients.
- A large scale multi-centre RCT is required to establish clinical and cost-effectiveness for KDs in glioma populations. The feasibility of running such a trial requires further exploration, given the apparent bias of self-selected, self-referring populations, utilised in the NHS scoping service and previous research (124,128,167).
- Motivations and barriers to participating in dietary trials and factors affecting dietary retention could be explored by qualitative means.
- Impact of KDs on quality of life should be explored through objective, validated measures.

3.7 CONCLUSION

KDs appear to be gathering momentum as an adjuvant therapy within the glioma patient population. The scoping study illustrates MKD for adults with gliomas to be deliverable within a dietetic-led, NHS service with no prior experience of KDs. The diet itself was tolerable, with limited side effects and there appears to be high levels of interest within the glioma patient community to ensure adequate recruitment would be possible within the context of a clinical trial. Whether MKD is an effective adjuvant therapy for glioma tumours remains to be proven. Further studies are required to establish clinical trial feasibility, following which an RCT could be established to investigate patient benefit. This will be required before the KDs are offered as a clinical service within the NHS.

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CHAPTER 4

KETOGENIC DIETS AS AN ADJUVANT THERAPY IN GLIOBLASTOMA (KEATING): A PROSPECTIVE, NON-BLINDED, RANDOMISED, PILOT TRIAL

4.1 CHAPTER OVERVIEW

Prior to undertaking a definitive randomised controlled trial (RCT) to determine the efficacy of ketogenic diets (KDs) as an adjuvant therapy for patients with glioblastoma (GBM), a feasibility study is required. This consisted of two parts; i) a pragmatic pilot trial to test protocol methodology in an NHS setting, to explore the potential impact of KDs on patient's quality of life and health; and ii) a qualitative study embedded into the pilot trial to explore patients' decision-making when invited to participate in the pilot (see chapter 5). The results of this feasibility study will inform the design of future KD trials for GBM.

This chapter focuses on the pilot trial KEATING and starts by introducing the role of feasibility and pilot studies in healthcare research, prior to exploring and justifying the methodology adopted for KEATING. Descriptive statistics are used to present the results at various time points in the trial. The chapter concludes by offering a discussion of the findings and recommendations for further research. The Consolidated Standards for Reporting Trials (CONSORT) extension for the reporting of pilot trials was utilised throughout this chapter (168).

The KEATING protocol (version 4, 20/DEC/2017) can be found in appendix H, along with associated documentation.

4.2 INTRODUCTION

Animal models have demonstrated KDs to be most effective when utilised alongside radiotherapy (79), but current evidence for patients is limited to case studies and one prospective pilot study (86,87,124–128), with no studies having utilised KDs prospectively, whilst the patient is receiving radiotherapy.

We have previously shown that KDs can be delivered within a dietetic-led NHS service (169) and that a proportion of patients with gliomas are interested in participating in a KD RCT (see chapter 3). However, prior to the design of a phase III RCT it is important to consider feasibility.

4.2.1 Feasibility and pilot designs

A feasibility study is defined by the National Institute for Health Research (NIHR) as a piece of research conducted before the main trial to understand if a trial can be undertaken. This feasibility phase allows researchers to identify and address problems that could undermine the acceptability and delivery of the intervention or conduct of the RCT (170). Parameters of interest that can be estimated by a feasibility study include eligibility rates, retention rates, compliance, response to questionnaires and completeness of data. Feasibility studies for RCTs do not necessarily follow the methods of the RCT, such as randomisation, and are not powered to assess efficacy. A feasibility study can include a pilot of the main trial and have a qualitative element (92).

A pilot trial is a version of the main trial, but on a smaller scale. As with feasibility studies, it is not powered to test efficacy, but instead is beneficial to explore recruitment rates, retention rates and if the trial protocol is sufficient and can be adhered to, by both the research team and participants (170). A pilot trial can be internal or external to the main trial.

This form of prior investigation, whether via a pilot or a feasibility study is recommended by the Medical Research Council (MRC) and NIHR Health Technology Assessment (HTA) programme, prior to full evaluation (171). A set of predefined success criteria for the preliminary study are recommended; if no problems exist or exist but are addressable by protocol modifications, the study can progress to a full RCT, or if fundamental problems exist the study would return to a development phase (172). For clinical trials, the two main concerns often relate to recruitment and retention of participants.

Recruitment to trials can be difficult due to a variety of reasons. For physicians, barriers such as a dislike of trial protocol, concerns with physician-patient relationship, time limitations, gaining informed consent, poor impression of the scientific merit, demographic and socioeconomic disparities affect their willingness to recruit (173–176). For prospective participants, the decision to participate can be influenced by personal values, family values, concerns with trial protocol, physician bias or lack of equipoise, health literacy, personal benefits, acceptability of the intervention, quality of life and side effects related to the intervention (106,174,175).

Despite improvements to recruitment practices for HTA and MRC funded trials since the 1990s (177), recruitment success continues to hinder clinical trials with only 56% meeting pre-defined targets between 2004 and 2016 (178) and fewer than one in twenty adult patients with cancer enrolling in a clinical trial (173). To compensate poor recruitment rates, the recruitment period is often extended, requiring additional time extensions and grant support, alternatively the recruitment target is reduced affecting the validity of the results and implementation into routine clinical practice (177,178).

Retention within trials is also important, with high levels of attrition reducing power and potentially introducing bias to trials (179). The median retention rate of patients for HTA funded trials between 2004 and 2016 was 89%, with retention defined at the point whereby the primary outcome was assessed (178). Factors influencing retention vary by trial, but can be related to patient expectations, motivation, demographics, time commitments, engagement and ongoing communication by the trial team (180,181).

4.2.2.1 Feasibility studies in dietary trials

Feasibility designs are currently being used to investigate dietary interventions in other fields, such as malnutrition in care homes (182) and the Mediterranean diet in human immunodeficiency viruses (HIV) dyslipidaemia (183), with pilot studies recently published for KD in Alzheimer's disease and migraine (67–69). There is no prior evidence of feasibility of KDs for patients with newly diagnosed GBM.

4.2.2 Selecting KD interventions for KEATING

In chapter three, we showed that the delivery of KDs within an NHS setting was possible using the modified ketogenic diet (MKD). Since that temporary service was initiated, developments in the area have led to the exploration of using medium chain triglyceride ketogenic diets (MCT KD) in oncology, with MCT KD being as effective as a 6:1 CKD in animal

models with human glioblastoma tumour line (83,84). MCT KD also offers the potential benefits of palatability, reduced blood glucose levels (87,119) and being nutritionally complete (see table 4.1) (84). Therefore, when designing KEATING, the opportunity was sought to include both MCT KD and MKD given there is little prior evidence of dietary acceptability, recruitment rates or dietary retention rates in ketogenic-oncology trials using either diet. Equipoise existed between the diets; it was not known which, if any, would be of benefit to patients with GBM or which would be better tolerated.

The relative strengths and weaknesses of MCT KD as presented in table 4.1.

Table 4.1: Summary of the strengths and weaknesses for using MCT KD in GBM

Diet	Strengths	Weaknesses
MCT KD	• Used in paediatric drug-resistant epilepsy since 1970s. • Animal models demonstrate efficacy of MCT KD to the same extent as 6:1 CKD and in comparison to controls (83,84). • Can reduce blood glucose levels (87,119). • Can be nutritionally complete when implemented with a dietitian. • Offers adequate protein for use in adult oncology patients in a hypermetabolic state (0.17-0.25g nitrogen/kg/day (147)) and meet the WHO safe protein intake (0.83g protein/kg/day (148). • MCT allows for an increased amount of dietary carbohydrate, which aids palatability.	• Most beneficial 'dose' of MCT unknown. • Limited evidence for use of MCT KD in adults; compliance and tolerability unknown. • Ketogenic (MCT) nutritional products create an additional cost to the NHS as only available via prescription. • MCT products can result in gastrointestinal discomfort e.g. constipation; diarrhoea. • Requires some skill with weighing/ quantifying portion sizes.

Abbreviations: CKD = classical ketogenic diet; MCT KD = medium chain triglyceride ketogenic diet; WHO = World Health Organisation.

A diet protocol was designed to standardise procedures, enabling comparability of the diets. In MCT KD, the amount of MCT incorporated into the diet varies (21-80% of estimated total energy requirements) and a pre-defined protocol did not exist. Table 4.2 provides a summary of the macronutrient content of MCT KD used in oncology; eight published studies were identified (six animal models (60–62,83,84,184), two human studies (119,185)) and one ongoing trial (139)).

Table 4.2: Comparison of the macronutrient content of MCT KD in oncology.						
Classification	**Study**	**Population**	**LCT fat** (% total energy)	**MCT fat** (% total energy)	**Carbohydrate** (% total energy)	**Protein** (% total energy)
Published animal studies	Tisdale et al. (1988)(62)	Mice: murine colon adenocarcinoma MAC16	U	68	U	U
	Beck et al. (1989) (184)	Mice: murine colon adenocarcinoma MAC16	U	80	U	U
	Otto et al. (2008)ǂ(60)	Mice: human gastric cancer cell line 23132/87	35.5	21.45	0.2	13
	Hao et al. (2015)*(61)	Mice: human colon cancer cell line HCT116	32.8	36.2	3	20
	Martuscello et al. (2015)(84)	Mice: human glioblastoma cells	30	30	10	30
	Aminzadeh-Gohari et al. (2017) (83)	Mice: human neuroblastoma cell lines SH-SY5Y, SK-N-BE(2)	49.6	25	1	8.1
Published human studies	Fearon et al. (1988)(186)	Adult cachexia (lung, gastric, ovarian); n=5	0	70	16	14
	Nebeling et al. (1995)(87,119)	Paediatric gliomas; n=2	10	60	20	10
Ongoing human studies	Ghodsi et al. (2012)(139)	Adult GBM; target n=20	U	50	U	U

ǂData as presented by authors. *7.5% accounted for as fibre and micronutrient supplements. Abbreviations: GBM = Glioblastoma; LCT = long chain triglyceride; MCT = medium chain triglyceride; U = unknown.

The MCT KD regimes noted in table 4.2 were diverse and so the evidence of MCT KD from paediatric literature was consulted for further comparison. Here, the MCT content varied between 30 to 60% (187–189). Table 4.3 presents the macronutrient content of the three most widely used MCT KD dietary regimes in the UK (190).

Table 4.3: Comparison of the macronutrient content of MCT diets in epilepsy.

Study	**Population**	**LCT fat** (% total energy)	**MCT fat** (% total energy)	**Carbohydrate** (% total energy)	**Protein** (% total energy)
Huttenlocher et al. (1971) (188)	Paediatric epilepsy; n=12	11	60	19	10
Schwartz et al. (1989) (189)	Paediatric epilepsy; n=55	11	60	10	19
	Adult epilepsy; n=4	41	30	10	19
Neal et al. (2009) (187)	Paediatric epilepsy; n=145	30	45	15	10

Abbreviations LCT = long chain triglyceride fat; MCT = medium chain triglyceride fat.

After reviewing the literature, MCT KD for KEATING followed a 'supplemented' approach of 30% of total energy derived from MCT (84,189), with the aim of ensuring gastrointestinal tolerance.

A summary of the macronutrient content of MCT KD and MKD used within KEATING are highlighted in table 4.4. This was the starting point for the diets, from which 'fine tuning' took place to optimise ketosis for each individual patient.

Table 4.4: Comparison of the macronutrient content of the dietary interventions used in KEATING

Ketogenic diet	**LCT fat** (% total energy)	**MCT fat** (% total energy)	**Carbohydrate** (% total energy)	**Protein** (% total energy)
MKD[6]	80	0	5	15
MCT KD[7]	45	30	10	15

Abbreviations LCT = long chain triglyceride; MCT = medium chain triglyceride; MCT KD = medium chain triglyceride ketogenic diet; MKD = modified ketogenic diet.

[6] The macronutrient content of MKD was altered slightly from the scoping service (previously 70% fat and 20g carbohydrate) to aid standardisation across the two KD interventions for KEATING.

[7] As MCT offers the benefit of increased ketone production (per calorie of energy) compared to long chain triglyceride (LCT) fats due to their rapid absorption into the portal system (81,82), carbohydrate requirements are increased and fat reduced slightly.

A control arm was not used at this stage, although a multi-arm multi-stage trial design was considered for the inclusion of a control arm (95,96). However, the sample size required to run such a study was beyond that of which could be achieved by a single site within a limited time frame and was considered beyond the scope of this thesis. The scoping survey also illustrated that a trial including a control arm (no diet) may be difficult to recruit to at this early stage and as the acceptability and feasibility of KDs were being explored alongside standard treatment, rather than the feasibility of randomisation between diet and no diet, a control arm was not included.

4.2.3 Summary

KEATING consisted of two parts; a pilot trial and a qualitative study. To investigate the feasibility of KDs as an adjuvant therapy for patients with newly diagnosed GBM undergoing chemoradiotherapy a prospective, non-blinded, single-centre, randomised pilot trial was undertaken (93,94). To further inform issues with recruitment and dietary retention, a qualitative study was embedded into the pilot trial to explore patients' decision-making when invited to participate in KEATING (see chapter 5). Overall, KEATING would inform the feasibility and design of future KD trials for patients with GBM.

4.2.4 Aims and objectives

4.2.4.1 Aim

- To investigate protocol feasibility and impact on patients by comparing two KDs in an NHS setting, with a view to informing the design of future phase III clinical trials.

4.2.4.2 Primary objective

- To estimate dietary retention rate to assess if a phase III trial is feasible.

4.2.4.3 Secondary objectives

Protocol feasibility objectives to inform future study design and sample size calculations:

- Estimation of recruitment rates.
- Enrolment of patients (consent, randomisation, baseline screening) pre oncological treatments.
- Enrolment of patients (consent, randomisation, baseline, screening) during oncological treatments.

- Enrolment of patients (consent, randomisation, baseline, screening) post oncological treatments (within four months of surgical intervention).
- Long term dietary retention.
- Dietary adjustments required to achieve ketosis.
- Dietary compliance.
- MCT supplement compliance.
- Ketosis levels.
- Dietetic time required for each intervention.
- Protocol refinements required.
- Completeness of data for all trial outcomes.

Patient impact objectives to inform future study design:

- Quality of life.
- Food acceptability.
- Gastrointestinal side effects.
- Changes in biochemical markers.
- Anthropometric changes.

4.3 METHODOLOGY

4.3.1 Trial design

A prospective, non-blinded, single-centre, randomised pilot trial with patients allocated at a ratio of 1:1 to MCT KD or MKD.

4.3.1.1 Ethical approval

Ethical approval was granted by the North West - Greater Manchester West Research Ethics Committee (17/NW/0013). The trial was granted permission to proceed by the Sponsor University of Liverpool on 29th March 2017 and opened to recruitment 1st April 2017.

The trial was registered with the International Standard Randomised Controlled Trial Number registry (ISRCTN71665562) and ClinicalTrials.Gov (NCT03075514).

The National Cancer Research Institute (NCRI) Brain Tumour Clinical Studies Group (CSG) provided portfolio support following peer review.

4.3.1.2 Amendment 1

Due to initial slow recruitment rates, an amendment was implemented in July 2017 (protocol version 2, 28/JUN/2017) to expand the inclusion criteria for the trial, with a view to broadening the trial population, by including biopsy patients and those patients receiving radiotherapy or chemotherapy, rather than combined chemoradiotherapy only treatments. Initial figures relating to the number of people with GBM that were surgically resected annually at The Walton Centre NHS Foundation Trust (WCFT) and going on to receive chemoradiotherapy were found that have been overestimated, possibly affecting projected recruitment targets. Hence, by including biopsy patients and those receiving radiotherapy and/or chemotherapy the eligible population from which to recruit increased in size.

In addition, following initial feedback from patients approached about KEATING, the option to commence KD post radiotherapy was implemented with a view to promoting uptake. To minimise the effect of this change on data heterogeneity, patients were permitted to commence the diet post radiotherapy, but within four months of surgery, to ensure most patients would likely be receiving adjuvant chemotherapy when starting their KD. Given the evidence from animal models previously discussed, it was considered desirable to commence patients on KD concurrently with an oncological treatment. Details of the amendments to inclusion criteria are detailed in table 4.5.

Table 4.5: Amendments to inclusion criteria

Protocol version 1 inclusion criteria	**Protocol version 2 inclusion criteria**
Age ≥16 years	Age ≥16 years
Patient at WCFT	Patient at WCFT
Performance status ≤2 (157)	Performance status ≤2 (157)
Confirmed histological diagnosis of GB (WHO grade IV (6))	Confirmed histological diagnosis of GB **within last four months** (WHO grade IV, (6))
Undergone surgical resection of GB	Undergone surgical resection **or biopsy** of GB
Will go onto receive chemoradiotherapy	Will go onto receive **or is currently receiving or completed adjuvant oncological treatments (radiotherapy, chemotherapy** or combination chemoradiotherapy)

NB: Amendments highlighted in bold.

4.3.1.3 Amendment 2

The initial trial recruitment period was 12 months. However, as recruitment rates remained low six months into the trial, this amendment extended the recruitment period of the study by a further 12 months (24 month recruitment period in total), following recommendations from the Trial Steering Committee (TSC; see section 4.7) in December 2017 (protocol version 4, 20/DEC/2017).

In conjunction with this, a qualitative study was embedded to explore patients' decision-making when invited to participate in KEATING, by undertaking semi-structured interviews with a sub-sample of patients and their relatives/ carers. This would enable the design of bespoke strategies to optimise the decision-making of future patients invited to participate in ketogenic-glioblastoma trials (see chapter 5).

4.3.2 Participants

Patients were recruited from a single adult neuroscience site (WCFT), which receives approximately 100 new cases of GBM each year. The target population were adults with newly, diagnosed GBM. All patients considered for the trial were required to meet the following eligibility criteria:

4.3.2.1 Inclusion criteria

- Age ≥16 years.
- Patient at WCFT.
- Performance status ≤2[8] (157).
- Confirmed histological diagnosis of glioblastoma within last four months via surgical resection or biopsy[9] (WHO grade IV, (6)).
- Planned to receive or currently receiving or completed adjuvant oncological treatments (radiotherapy, chemotherapy or combination chemoradiotherapy)[10].
- A performance status of 2 or less was selected; ensuring patients were likely to receive adjuvant oncological treatments and were fit enough to attend clinic appointments[11].

[8] Performance status (PS) 0 is defined as normal activity; PS 1 is defined as some symptoms but nearly fully ambulant; PS 2 is defined as less than 50% daytime in bed; PS 3 is defined as greater than 50% daytime in bed; PS 4 is completely bed bound (157).

[9] A confirmed histological diagnosis of glioblastoma graded using the WHO criteria (6) was required to ensure a consistent sample.

[10] Patients were to be receiving or have received oncological treatments as animal models demonstrate the diet to be most effective at enhancing survival if commenced concurrently with oncological treatments, adjuvant to surgery (79,80).

[11] A time span of four months post-surgery was determined appropriate as this is the approximate time required to complete chemoradiotherapy (STUPP protocol (21)). However, courses of radiotherapy or chemotherapy alone were shorter in length.

4.3.2.2 Exclusion criteria

- Any prior use of a KD[12*].
- Kidney dysfunction (CKD III/IV, renal stones, cancer, low phosphate/potassium/salt diets)[13#].
- Liver dysfunction (alcoholic liver disease, non-alcoholic liver disease, cancer, hepatitis, haemochromatosis, primary biliary cirrhosis)[*].
- Gall bladder dysfunction (gallstones, cholecystectomy in past 12 months, cancer)[*].
- Metabolic disorder (carnitine deficiencies, β oxidation defects [medium chain acyl-CoA dehydrogenase deficiency, very long chain acyl-CoA dehydrogenase deficiency, short chain acyl-CoA dehydrogenase deficiency, long chain 3-hydroxyacyl CoA deficiency, medium chain 3-hydroxyacyl CoA deficiency], pyruvate carboxylase deficiency, porphyria)[*].
- Eating disorder (anorexia nervosa, bulimia nervosa, binge eating disorder)[*].
- Diabetes (requiring medication)[*].
- Body mass index (BMI) ≤18.5kg/m^2. [14*]
- Current use of weight loss medications (Orlistat, Belviq, Contrave, Saxenda, Phentermine, Qsymia)[15*].
- Currently pregnant or breastfeeding[16*].
- Performance status ≥3 (157)[*].
- Medical conditions that may increase risks associated with KD[*].

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[12] To minimise participant bias, patients with prior use of KDs were excluded.
[13] Diabetes, kidney, liver, gall bladder, metabolic and eating disorders are contraindications for the diet as recommended by the International Ketogenic Diet Study Group (293).
* Assessed through clinical history.
# Assessed via biochemistry.
[14] Underweight patients, defined as BMI less than 18.5kg/m^2, were excluded due to the risk of malnutrition and the possibility that nutrition support may be indicated (294).
[15] Weight loss medications such as orlistat are contraindicated in KDs due to the limitation in the absorption of fat, which could result in gastrointestinal issues.
[16] The effect of KD in pregnancy and breastfeeding women is uncertain (295), therefore these patients were excluded from the study.
* Assessed through clinical history.
# Assessed via biochemistry.

4.3.2.3 Screening and consent

Following a histological diagnosis of GBM, patients were referred to the trial by their neurosurgical team at the WCFT and the neuro oncology multi-disciplinary team (MDT) meeting, following initial discussions with a member of their clinical team. Patients were then telephoned by the trial dietitian who briefly discussed KEATING and provided a patient information sheet by post (see appendix J). Patients were re-contacted one week later and offered an information/ screening appointment, ensuring patients had adequate time to consider trial involvement.

At the information/ screening appointment, the trial dietitian discussed KEATING trial procedures and dietary interventions with the patient and their relative/carer (if present). Patients were provided with the opportunity to ask questions, following which written, informed consent was obtained. Baseline biochemistry tests were then undertaken to ensure eligibility for the trial.

4.3.3 Interventions

Two KDs were included in KEATING; MCT KD and MKD. A summary of the macronutrient content of each diet can be found in table 4.4 Patients and their relative/carer (if present) received dietary education from the dietitian and were provided with a bespoke seven day meal plan, recipes, dietary information sheets and food diaries (see appendices K, L, M). Patients could input into their diet by calculating their own MKD or MCT KD recipes and meal plans through the use of carbohydrate and fat 'choice lists'. A three-month dietary intervention was planned (primary end point), following which patients could choose to continue with the diet for a total of 12 months (secondary end point).

Both diets were commenced promptly, without fasting (191), at the patients' home (rather than hospital) to minimise costs and aid practicality. Those patients consuming MCT supplements were encouraged to titrate these to target dose over a one-week period, to aid dietary tolerance.

All KDs were calculated to the patients nutritional requirements using the British Dietetic Association (BDA) Parenteral and Enteral Nutrition Specialist Group (PENG) methods (192–198), with requirements being tailored for patient activity levels (194). Energy requirements were tailored for weight loss or maintenance dependent upon the patient's needs and wishes and were recalculated each time a new weight was obtained.

After calculating nutritional requirements, the KD was calculated based on the macronutrient content of the randomised diet (MKD or MCT KD, see table 4.6). This was known as the KD 'prescription'. MCT was delivered using Betaquik® (Vitaflo International Ltd, Liverpool, UK), a 'ready to drink' food for special medical purposes, the volume of which was calculated by the dietitian to provide a target of 30% of total estimated energy requirements.

Table 4.6: Example calculation for macronutrient content of KDs based on 48yr old male, weighing 78kg, requiring 2100kcals/day.

Macronutrient	MCT KD	MKD
LCT Fat	(2100kcals*45%)/9 = 105g/d[ł]	(2100kcals*80%)/9 = 187g/d[ł]
MCT Fat	(2100kcals*30%)/9 = 70g/d	0
Carbohydrate	(2100kcals*10%)/4 = 52g/d	(2100kcals*5%)/4 = 26g/d
Protein	(2100kcals*15%)/4 = 79g/d	(2100kcals*15%)/4 = 79g/d

NB: The energy yield of each macronutrient is as follows; fat 9.4kcals/g, protein 4.7kcals/g, carbohydrate 4.1kcals/g and MCT 9kcals/g (199).

Patients (and relatives/ carers when appropriate) were also educated in blood glucose, blood ketone and urinary ketone monitoring and target levels.

4.3.3.1 Timing of intervention

Patients commenced the diet within four months of surgical intervention (resection or biopsy), prior to, during or post the concurrent oncological intervention. All surgical and oncological interventions were undertaken as per current standard of care (200).

4.3.3.2 Dietetic monitoring and follow up

After starting the diet all patients were reviewed by telephone at weeks one, three and nine, and in an outpatients clinic at weeks six and twelve (primary completion of trial). Patients who wished to continue with the diet were then reviewed at six, nine and twelve months (secondary completion of trial); providing long term data. Table 4.7 provides further information of assessments and figure 4.1 presents a schematic of the trial design.

Patients were requested to monitor urinary ketones twice daily for the first six weeks, then weekly thereafter using Ketostix® (Bayer, Germany). Blood ketones and glucose levels were monitored once weekly using GlucoMen Aero 2K® home monitoring kit (Abbott Laboratories, UK).

At each time point the dietitian would compare ketone levels to dietary intake and recommend adjustments to the diet (when required) to improve ketone levels,

gastrointestinal tolerance, compliance and dietary acceptability; alongside modifications required due to alterations in anthropometry (such as weight).

The dietary trial period was completed at twelve months and those patients wishing to continue with the diet after this time were offered three monthly follow up with the dietitian.

Table 4.7: Assessments and time scales for KEATING											
Timeline		1 week post histology	1 week after clinic 1	1 weeks after clinic 2	3 weeks after clinic 2	6 weeks after clinic 2	9 weeks after clinic 2	12 weeks after clinic 2	6 months after clinic 2	9 months after clinic 2	12 months after clinic 2
Visit window	Post histology		±5 days	±3 days	±3 days	±5 days	±3 days	±5 days	±10 days	±10 days	±10 days
Clinic visit	Telephone and information sheet	Clinic appointment 1 Consent, register, baseline assessment, randomisation	Clinic appointment 2 Commence diet	Telephone review 1	Telephone review 2	Clinic appointment 3 Diet review	Telephone review 3	Clinic appointment 4 Diet review	Clinic appointment 5 Diet review	Clinic appointment 6 Diet review	Clinic appointment 7 Diet review End of trial
Informed consent		X									
Eligibility screen		X									
Randomisation		X									
Medical history review*		X									
Medications review		X									
Anthropometry		X				X		X	X	X	X
Biochemistry		X						X	X	X	X
Food diary		X				X		X	X	X	X
Ketone diary						X		X	X	X	X
QoL questionnaire EORCT QLQ C30		X				X		X	X	X	X
QoL questionnaire QLQ BN20		X				X		X	X	X	X
Food Acceptability Questionnaire		X				X		X	X	X	X
Dietary review ǂ		X	X	X	X	X	X	X	X	X	X
Ketone review				X	X	X	X	X	X	X	X

Abbreviations: QoL= Quality of life. NB: *Including tumour location, surgical procedure, histopathology and molecular pathology subtypes for glioblastoma (MGMT, IDH-1, ATRX, 1p/19q status). ǂ Including nutritional supplementation, food allergies, level of physical activity, nutritional requirements, gastrointestinal complaints, food/fluid modification, use of clinically assisted nutrition.

Figure 4.1: Schematic of trial design

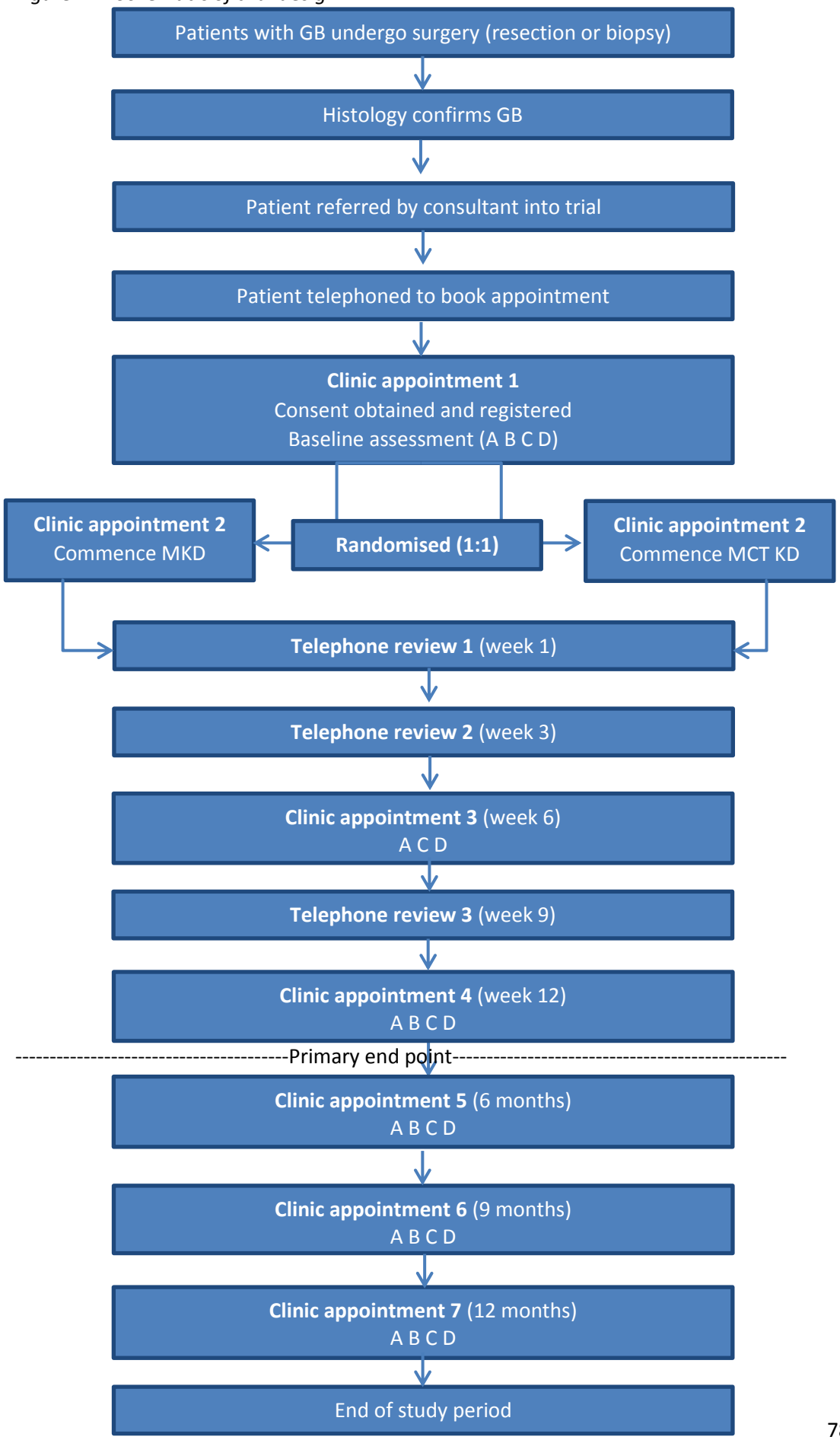


Table 4.8: Schematic of trial design key	
A	Anthropometry (weight, height, waist circumference, fat mass, body mass index [BMI], hand grip strength [HGS], mid arm muscle circumference [MAMC])
B	Biochemistry (renal, bone, liver function test (LFT), fasting lipid, fasting glucose)
C	Collect food and ketone diaries
D	Quality of life and food acceptability questionnaires

*Patients are able to telephone between appointments should further dietary support be required.

4.3.4 Outcomes

4.3.4.1 Primary outcomes

Assessment of dietary retention and drop-out rates, defined as:

I. The number of patients who start randomised treatment as a proportion of the number randomised, with reasons for non-compliance.
II. The number of patients who complete three months of diet as a proportion of the number randomised, with reasons for non-compliance.
III. The time to dietary discontinuation.

4.3.4.2 Secondary outcomes: protocol feasibility

I. Estimation of recruitment rates

Actual recruitment rates (over 24 months) were compared to proposed recruitment figures (12 patients over 12 months) with purpose of demonstrating trial feasibility for future, potential phase III clinical trials.

II. Enrolment of patients

Ability to comply with protocol enrolment time lines assessed by the number of patients initiated on diet prior to, whilst receiving, and post oncological treatment. This will inform the feasible time lines in future clinical trials.

III. Long term dietary retention

Duration to dietary discontinuation after three months.

IV. Dietary adjustments required to achieve ketosis

Dietary adjustments required from baseline to achieve ketosis to inform future protocols.

V. Dietary compliance

Percentage compliance with fat and carbohydrate targets, calculated through patient food diaries and compared to predefined fat and carbohydrate requirements.

VI. MCT compliance

VII. Percentage compliance with MCT targets, calculated through patient food diaries and compared to predefined MCT supplement volume. Ketosis levels

Adequate urinary ketosis defined as ≥4mmol/L.

There are no robust guidelines for adequate levels of blood ketosis in adults with GBM. Preliminary work suggests levels of 2-4mmol/L to be beneficial (146). Patients were asked to record levels to aid future research.

VIII. Dietetic time required for the interventions

Dietetic time spent on both clinical and non-clinical activities related to the trial was recorded at each contact to aid future protocol design.

IX. Protocol refinements required

Deviations from the protocol were documented on the deviation log. This will be used to refine future protocols and inform future clinical trials.

4.3.4.3 Secondary outcomes: impact on patients

I. Quality of life

Quality of life was evaluated though the European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire (QLQ) QLQ-C30 and QLQ-BN20 prior to commencing the diet, at week six, month three and every three months thereafter.

II. Food acceptability

Food acceptability was assessed through the Food Acceptability Questionnaire (201) completed prior to commencing the diet, at week six, month three and every three months thereafter.

III. Gastrointestinal side effects

The Common Terminology Criteria for Adverse Events ([CTCAE], version 4.0) was used to grade gastrointestinal side effects documented on the CRF at each dietetic contact, following a baseline evaluation.

IV. Changes to biochemical markers

Biochemical markers (fasting lipid, fasting glucose, liver, renal and bone profiles) were undertaken at baseline and repeated three monthly until discontinuation of diet.

V. Anthropometric changes

Anthropometry (height, weight, body mass index (BMI), waist circumference, mid upper arm circumference (MUAC), mid arm muscle circumference (MAMC), tricep skin fold (TSF)[Body

Care, UK], hand grip strength (HGS) [Takei, Japan] and fat mass [Omron, Japan]) were measured at baseline, week six, month three and every three months thereafter. All measurements were undertaken as per measurement methodology cited in BDA PENG, pocket guide to clinical nutrition (198).

VI. Completeness of data for all trial outcomes

Completeness of documented data was assessed to inform feasibility of future clinical trials.

4.3.4.4 Defining success

Little guidance is available from which to define the success of an external pilot or feasibility study like KEATING. Therefore, pilot success for KEATING was graded using a predetermined traffic light system designed for use in internal pilots, which considered recruitment success, dietary retention rates, extent of missing data, dietary acceptability and the commencement of diet pre chemoradiotherapy (172).

Targets for determining success were discussed with the Trial Monitoring Committee (TMC) and funder. Targets were considered aspirant for the trial team to achieve, yet flexible in allowing for amendments during the study and were reviewed monthly by the TMC and quarterly by the TSC.

Success criteria were as follows[17]:

Green (go):

- Recruitment rate of ≥75% of target (n=9) achieved within the 12 month recruitment period.
- ≥75% of patients commenced KD prior to chemoradiotherapy.
- Dietary retention rate of ≥75% at three months.
- Diet acceptable to ≥75% of patients at three months.
- ≥75% of the proposed data collection completed for each end point.

Amber (review):

- Recruitment rate of ≥50% of target (n=6) achieved within the 12 month recruitment period.

[17] Retention rate, dietary acceptance and data collection were assessed for each diet independently. Recruitment rate and dietary commencement were assessed using data combined from both arms.

- ≥50% of patients commenced KD prior to chemoradiotherapy.
- Dietary retention rate of ≥50% at three months.
- Diet acceptable to ≥50% of patients at three months.
- ≥50% of the proposed data collection completed for each end point.

Red (stop):

- Recruitment rate <50% of target (n=5) achieved within the 12 month recruitment period.
- <50% of patients commenced KD prior to chemoradiotherapy.
- Dietary retention rate of <50% at three months.
- Diet acceptable to <50% of patients at three months.
- <50% of the proposed data collection completed for each end point.

Components of the pilot considered not feasible or unacceptable to patients were evaluated (amber and red criteria above) (202) and the ADePT method was used to evidence the decision making process (see section 4.5.2) (203). Recommendations were devised for consideration by phase III KD trials for patients with GBM in keeping with the CONSORT guidelines (see section 4.5.2) (168).

4.3.5 Sample size

UK pilot studies have been found to have a median sample size of 30 participants (range 8-114 participants) (204), with sample sizes of 10-40 participants considered to be statistically adequate (205). Previous feasibility work estimated recruitment targets of one patient per month (169), in keeping with NIHR/HTA funded trials (178). As this study was being conducted as part of a PhD thesis the recruitment period was limited to 12 months, therefore the recruitment target was set at 12 patients over this time frame.

Results of the scoping service (chapter 3) demonstrated a likely dietary retention rate of 70% at three months (169). With a sample size of 12, it was possible to estimate retention rates of 70% to within a 95% confidence interval of ±25.93% (206). Whilst the confidence interval may be broad at present, data synthesised from this pilot will inform sample size estimates for future, phase III clinical trials.

4.3.6 Randomisation

Once biochemistry was returned and if within range, the patient was randomised to either MCT KD or MKD using the 'sealedenvelope'™ randomisation system and a permuted block randomisation method, to ensure similar numbers in each group, at a ratio of 1:1. This was set up and administered by the trial statistician, who was not involved with recruiting patients. Patients were then informed of their dietary intervention group by telephone and initiated diet within five working days of consent.

4.3.7 Procedures for assessing efficacy

Efficacy was not determined from this trial due to the limited sample size (168). However, Magnetic Resonance Imaging (MRI) was used to interpret tumour progression and progression free survival for those patients enrolled on the study.

Progression free survival was defined as the time from date of randomisation to date of recurrence on MRI. Recurrence was defined by a Neuroradiologist using the Response Assessment in Neuro-Oncology (RANO) criteria (207). Progression free survival data was assessed by Kaplan-Meier survival analysis.

Overall survival was defined as the time from date of randomisation to date of death from any cause.

4.3.8 Safety

4.3.8.1 Terms and definitions

Adverse event (AE): is any unexpected situation that takes place during the course of the trial. An AE may be related to the dietary intervention or an unrelated cause.

Serious adverse event (SAE): an event which results in death, is life threatening, requires hospital admission or prolongs hospital stay, results in significant or persistent disability or incapacity or results in a birth defect.

Life threatening: potentially fatal illness or injury at time of occurrence.

Related: resulted from the administration of the dietary intervention.

Unexpected: type of AE or SAE not listed on the protocol and is not a likely occurrence.

4.3.8.2 Adverse event inclusions and exclusions

Inclusion:

- Injury or accident
- Abnormalities in biochemistry that require further investigation or treatment
- Exacerbation of a pre-existing illness
- Development of an illness during the trial
- Worsening of baseline symptoms

Exclusion:

- Previously planned hospital admission
- Past medical conditions that do not worsen with intervention
- Medical or surgical procedures undertaken due to the adverse event
- Elective cosmetic surgery
- Gastrointestinal side effects unless resulting in hospital admission
- Altered lipid profiles unless resulting in the commencement of lipid lowering medication or further investigations

The Common Terminology Criteria for Adverse Events ([CTCAE], version 4.0) was used to grade AEs. All SAEs were reported to the Heath Research Authority (HRA) Research Ethics Committee (REC).

4.3.9 Statistical analysis

Descriptive statistical methods have been used and a Kaplan-Meier survival curve was estimated for overall survival and progression free survival and displayed graphically with 95% confidence intervals. Quality of life was assessed according to the EORTC QLQC30 and BN20 scoring manual (208).

Adverse events (AE) and serious adverse events (SAE) were reported as per CONSORT for pilot and feasibility studies (168).

4.3.9.1 Post-hoc analysis

Over the course of the trial, dietary retention became an issue. Therefore, a sub analyses was introduced at week six for primary and secondary outcomes, with a view to providing further information which would inform the design of later trials. In addition, the global health status of patients (EORTC QLQC30) was analysed comparing those who withdrew and

those who retained within each diet (MCT KD and MKD). This was not included in the protocol. This study was funded via a PhD studentship from Vitaflo (International) Ltd. The funder had no input into the analysis or interpretation of the study findings.

4.3.10 Patient and public involvement

Patients and their relatives/ carers from the scoping service were invited to attend a patient and public involvement (PPI) focus group during the design phase of KEATING, led by the trial dietitian. Their active involvement was sought in identifying research priorities and outcome measures for the use of KDs for patients with GBM. Their opinion was also sought for improvements required to patient information leaflets, recruitment processes, clinic appointments and reducing patient costs to enhance trial participation. The ideas and opinions from the PPI group were developed and incorporated into the protocol and supporting patient information sheets, with the plain language summary meeting their approval.

4.4 RESULTS

4.4.1 Participant characteristics

Fifty seven patients were screened for eligibility between April 2016 and March 2017. Of these, 15 were ineligible (26.3%), 30 declined (52.6%) and 12 (21.1%) were recruited to participate in KEATING. Of those recruited eight were male and four female, with a median age of 57 years (44 – 66 years). Three patients had undergone a gross total resection, six a near total resection, one a sub-total resection and two a biopsy, prior to commencing chemoradiotherapy. Four patients had *O^6-methylguanine-DNA methyltransferase (MGMT)* promoter methylation status. Follow up was at 12 months from the date of commencing the diet. Figure 4.2 depicts patient flow through the trial and table 4.9 presents the demographic and clinical characteristics of patients who participated.

Figure 4.2: CONSORT diagram

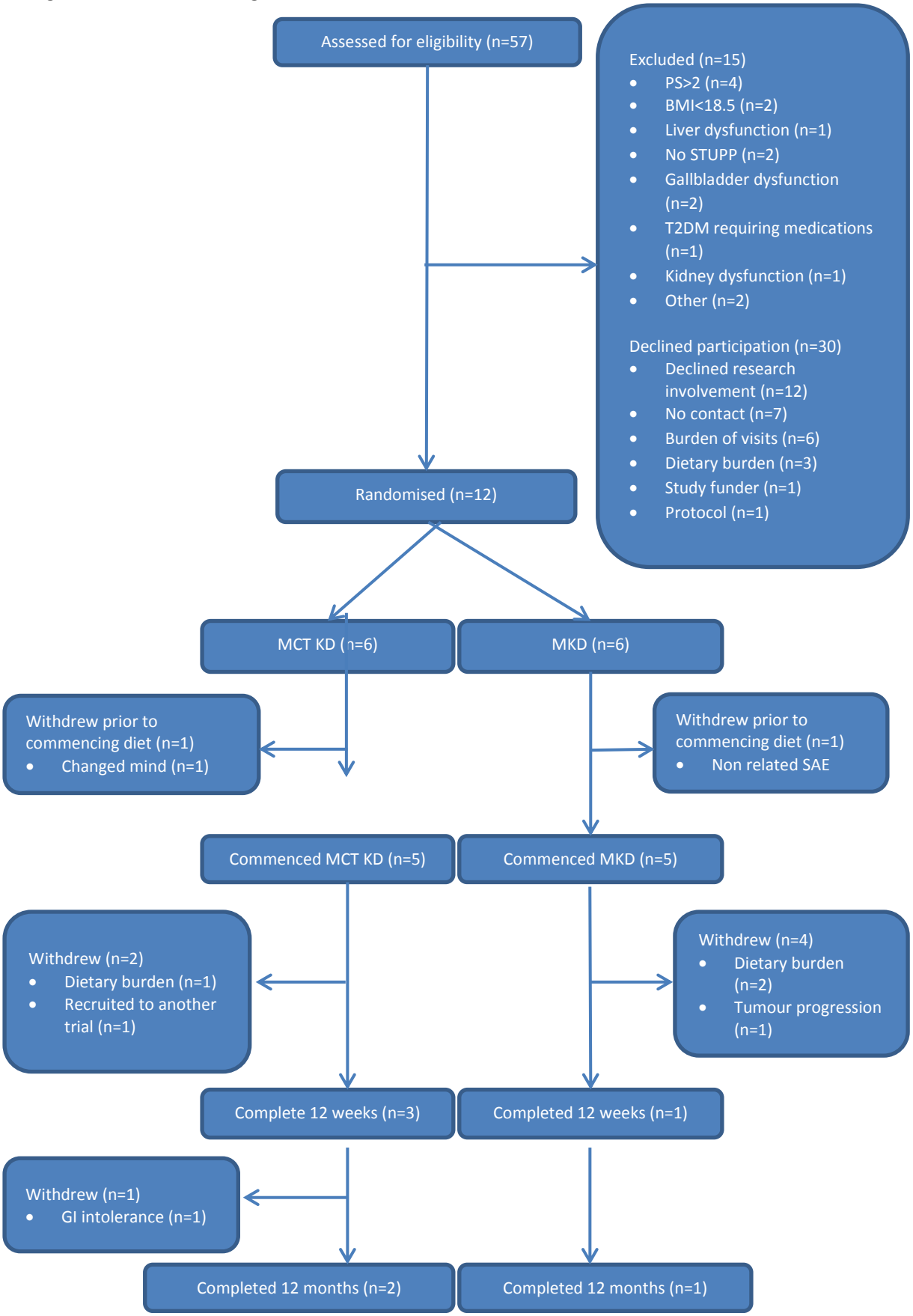


Table 4.9: Patient demographics and clinical characteristics

Trial N°.	Gender	Age (yrs)	Tumour location	Treatment	Pathology			DEX (mg/d) (median [range])	Study arm	Duration on diet (weeks)	PFS (weeks)	OS (weeks)
					MGMT	*IDH-1*	*ATRX*					
T01	Male	53	Right temporal	GTR, RT, TMZ	Unmethylated	Wildtype	Retained	5 (2-4)	MCT KD	22.4	32.4	35.4
T13	Male	49	Left parietal	NTR, RTX, TMZ	Unmethylated	Wildtype	Retained	4 (0)	MCT KD	5.1	14.4	60.6
T23	Female	54	Left frontal	NTR, RTX, TMZ	Unmethylated	Wildtype	Retained	4 (0)	MCT KD	5.7	44.4	83.6
T27	Female	62	Right occipital	GTR, RTX, TMZ[b]	Methylated	Wildtype	Retained	2 (0)	MKD	0	5.1	NA[e]
T28	Male	64	Left temporal	Bx, RTX, TMZ[a]	Unmethylated	Wildtype	Retained	4 (3-4)	MKD	7	13.1	67.3
T39	Female	66	Right parietal	NTR, RTX, TMZ	Methylated	Wildtype	Retained	4 (0)	MKD	5.3	64.3	NA[e]
T44	Male	44	Right temporal	GTR, RTX, TMZ	Methylated	Mutated	Mutated	NA	MKD	52	NA[d]	NA[e]
T45	Male	46	Left frontal	NTR, RTX, TMZ, Lomustine	Unmethylated	Wildtype	Retained	3 (2-3)	MCT KD	52	14.0	NA[e]
T47	Female	58	Right frontal	NTR, RTX, TMZ[a]	Inconclusive[c]	Wildtype	Retained	2 (0)	MKD	4.6	14.0	31.6
T51	Male	57	Left frontal	STR, RTX, TMZ	Methylated	Mutated	Mutated	1 (1-1.5)	MCT KD	52	NA[d]	NA[e]
T52	Male	60	Left frontal	NTR, RTX, TMZ[a]	Unmethylated	Wildtype	Retained	2 (0)	MCT KD	0	23.9	NA[e]
T57	Male	57	Right multifocal	Bx, RTX, TMZ[a]	Unmethylated	Wildtype	Retained	2 (0)	MKD	6	14.0	57.1

Abbreviations: *ATRX* = *alpha thalassemia/mental retardation syndrome X linked;* Bx = biopsy; DEX = dexamethasone; GTR = gross total resection; MCT KD = medium chain triglyceride ketogenic diet; *MGMT* = *O^6-methylguanine-DNA methyltransferase;* MKD = modified ketogenic diet; NA = not applicable; ND = no data recorded by patient; NAe = not applicable (alive at time of reporting); NTR = near total resection; OS = overall survival; PFS = progression free survival; RTX = radiotherapy; SD = standard deviation; STR = subtotal resection; TMZ = temozolomide; Treatment = treatment received whilst following a ketogenic diet; [a] = unknown if completed full course of radiotherapy and chemotherapy as withdrew from trial; [b] = 6 days of temozolomide not given; [c]= insufficient tissue to perform *MGMT* analysis; [d]= no progression at time of reporting (08/MAR/2019); [e]= alive at time of reporting (08/MAR/2019).

4.4.2 Primary outcome

4.4.2.1 Dietary retention at three months

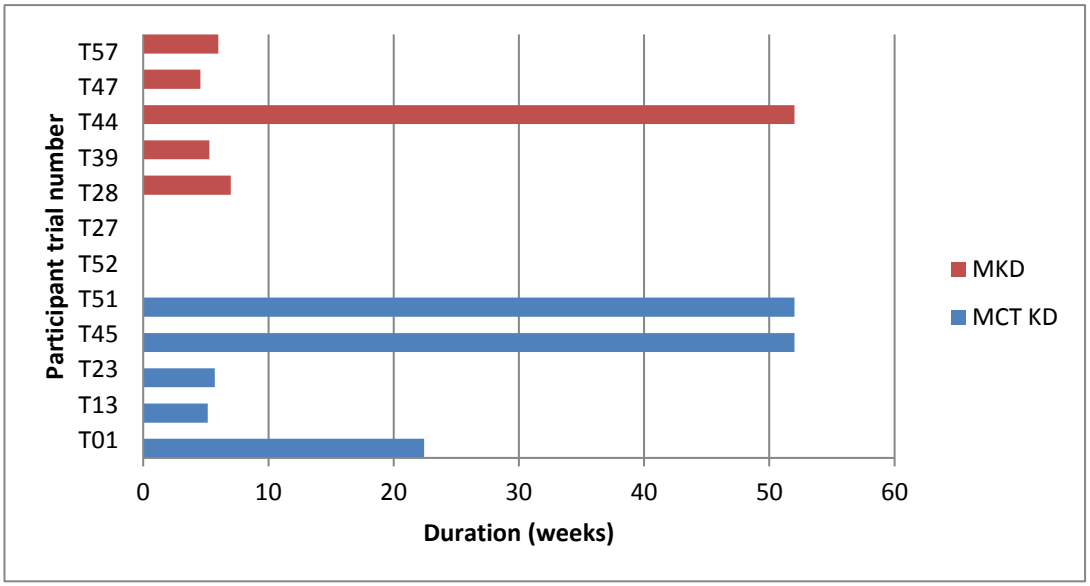
Of the 12 patients recruited to KEATING (n=6 MCT KD; n=6 MKD), two withdrew following randomisation but prior to commencing the diet (n=1 MCT KD; n=1 MKD). Reasons for withdrawal were a non-dietary related SAE (n=1) and a patient changing their mind about participating (n=1).

Of the 10 patients who commenced diet, six withdrew prior to reaching the three month primary end point (n=2 MCT KD; n=4 MKD). Reasons for withdrawal from the MCT KD group were dietary burden due to diet and supplement intolerance (n=1) and having been recruited to another trial (n=1; Novo Tumour Treating Fields trial). Patients' reasons for withdrawal from the MKD group were dietary burden due to high fat nature of diet (n=2), nausea (n=1) and early tumour progression (n=1). The median duration until discontinuing the diet was 38 days (36-40 days; n=2) for the MCT KD group and 39.5 days (32-49 days; n=4) for the MKD group.

Six patients stayed on diet until week six, after which four continued for a total of three months (n=3 MCT KD; n=1 MKD). All four of these patients then continued with their allocated KD beyond three months. A summary of patient flow is presented in figure 4.2 and figure 4.3 illustrates dietary retention throughout the course of the trial.

The predefined, lower limit criteria for successful retention was 50%. The overall dietary retention rate at three months for KEATING was 33.3%.

Figure 4.3: Dietary retention during KEATING



NB: T27 and T52 withdrew prior to commencing the diet.

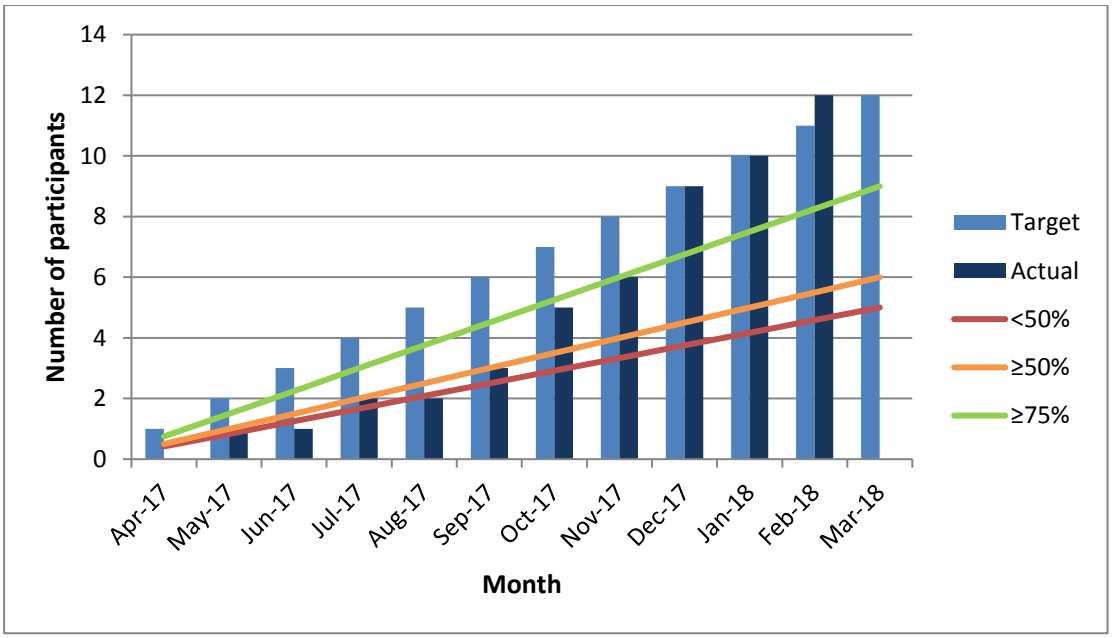
4.4.3 Secondary outcomes: Protocol feasibility

4.4.3.1 Recruitment

Twelve patients were recruited from a sample of 42 eligible patients, achieving a recruitment rate of 28.6% (or 21% of the overall screened population). Reasons for declining participation included the patient declining research involvement (n=12), the research team being unable to contact patient (n=7), the burden of visits (n=6), the burden of diet due to restriction of carbohydrate foods (n=3), the study funder (due to Nestle [the parent company of the trial sponsor Vitaflo] previously funding powdered baby milk research; n=1) and the trial protocol was unagreeable (n=1), see figure 4.1.

During the first six months, recruitment was in keeping with the predefined mid-limit of 50%, recruiting three patients (see section 4.3.1.2 for amendments). During the final six months recruitment improved, exceeding the predefined, higher recruitment target of 75%; recruiting 12 patients over 12 months. Figure 4.4 shows recruitment over the 12 month period, in comparison to predefined recruitment targets and recruitment success criteria.

Figure 4.4: Recruitment tracker



Abbreviations: Target = target number of patients to recruit each month as a total aggregate total; Actual = actual recruitment each month as a total aggregate; <50% = lower limit predefined recruitment target; ≥50% = mid-limit predefined recruitment target; ≥75% = higher predefined recruitment target.

4.4.3.2 Enrolment of participants prior to, during and post chemoradiotherapy commencement

All patients (n=12) were enrolled and consented prior to starting chemoradiotherapy.

Three patients commenced KD before starting chemoradiotherapy (n=3 MKD), seven during chemoradiotherapy (n=5 MCT KD, n=2 MKD; median delay 5 days [3-16 days]; delay at patients request due to oncology appointments) and no patients commenced diet after completing chemoradiotherapy.

The predefined lower limit criteria for enrolment and dietary commencement were 50%. During KEATING, 30% of patients (n=3) commenced KD prior to chemoradiotherapy.

4.4.3.3 Long term dietary retention

Of the 12 patients recruited to KEATING, four continued with their KD after month three (n=3 MCT KD; n=1 MKD). One patient (MCT KD group) then stopped at month six due to gastrointestinal side effects. In total, three patients completed the 12 month intervention period (n=2 MCT KD; n=1 MKD). These patients all chose to continue with their KD after completing the trial.

4.4.3.4. Dietary adjustments required to achieve ketosis

Four patients required dietary adjustments from baseline calculations to improve ketosis. These changes took place during the first six weeks following dietary initiation. All four patients were in the MCT KD group. For two patients, carbohydrate intake was reduced (mean -10.5g/d; standard deviation [S.D] ±7.4g/d) and long chain triglyceride (LCT) fat increased (mean 6g/d; S.D. ±2.8g/d); for one patient carbohydrate intake reduced (-10g/d) and medium chain triglyceride (MCT) fat increased (15g/d); and for one patient LCT was exchanged for MCT (15g/d).

4.4.3.5 Dietary compliance

Dietary compliance was assessed at week six (n=4 MCT KD and n=4 MKD), week 12 (n=3 MCT KD and n=1 MKD) and at month 12 (n=1 MCT KD) on the basis of returned food diaries. At week six, patients following MCT KD achieved their fat (LCT) target (mean -0.6%; S.D. ±4.6%) and those following MKD over consumed fat (LCT) (mean 12.4%; S.D. ±3.2%). The MCT KD group over consumed carbohydrates (mean 45.4%; S.D. ±1.3%) and MKD group under consumed carbohydrate (mean -9.6%; S.D. ±0.4%) compared to their calculated macronutrient requirements.

At month three, patients following MCT KD (n=3) over consumed fat (LCT) (mean 69.9%; S.D. ±3.1%); but these patients had reduced their intake of MCT (see section 4.4.3.4). The patient (n=1) following MKD under consumed fat (14%). At this stage, both groups under consumed carbohydrate (MCT KD mean -45.8% S.D. ±10.5%; MKD -71.5%).

At month 12, one patient over consumed fat (LCT) by 21.2% and under consumed carbohydrate by 32.7% compared to their calculated macronutrient requirements (n=1); whilst three patients completed the 12 month trial period only one patient completed a food diary.

The extent to which this over and under consumption of macronutrients affected the balance of the diets is presented in table 4.10. In the MCT KD group the consumption of LCT fat increased over the course of the trial and whilst MCT fat reduced (see section 4.4.3.6). For MKD, the consumption of fat (LCT) remained static throughout. Carbohydrate consumption reduced over time in both groups, with an increase at month 12 in MCT KD (n=1).

Table 4.10: Average macronutrient consumption over duration of trial

		Macronutrient			
Diet	**Time point**	**Fat (LCT) (%TEI)**	**Fat (MCT) (%TEI)**	**Carbohydrate (%TEI)**	**Protein (%TEI)**
MCT KD	Initiation target	45	30	10	15
	Week 6 (n=3)	50	26	8	16
	Month 3 (n=3)	59	25	5	11
	Month 12 (n=1)	65	16	7	12
MKD	Initiation target	80	NA	5	15
	Week 6 (n=3)	81	NA	3	16
	Month 3 (n=1)	80	NA	3	17

Abbreviations: LCT = long chain triglyceride; MCT KD = medium chain triglyceride ketogenic diet; MKD = modified ketogenic diet; TEI = percentage of total energy intake. NB: Macronutrients based upon completed and returned food diaries. One patient following MKD completed 12 month follow up but did not complete food diary, therefore no data is available for this time point.

4.4.3.6 MCT compliance

MCT compliance was assessed at week six (n=4), month three (n=3) and month 12 (n=2). At week six, three patients were 100% compliant with the volume of MCT and one patient was under consuming the supplement by 28.6%. At month three, one patient was 100% compliant and two patients were under consuming the MCT supplement by 21.1% (S.D. ±12.1%). At month 12, the both patients were under consumed the supplement by an average of 26% (S.D. ±13%; n=2). Reasons for non-compliance were reported as excessive volume by all patients affected at each time point (n=3).

On average, the total energy intake provided by MCT supplements reduced over the duration of the trial (see table 4.10).

4.4.3.7 Level of ketosis

Urinary ketosis

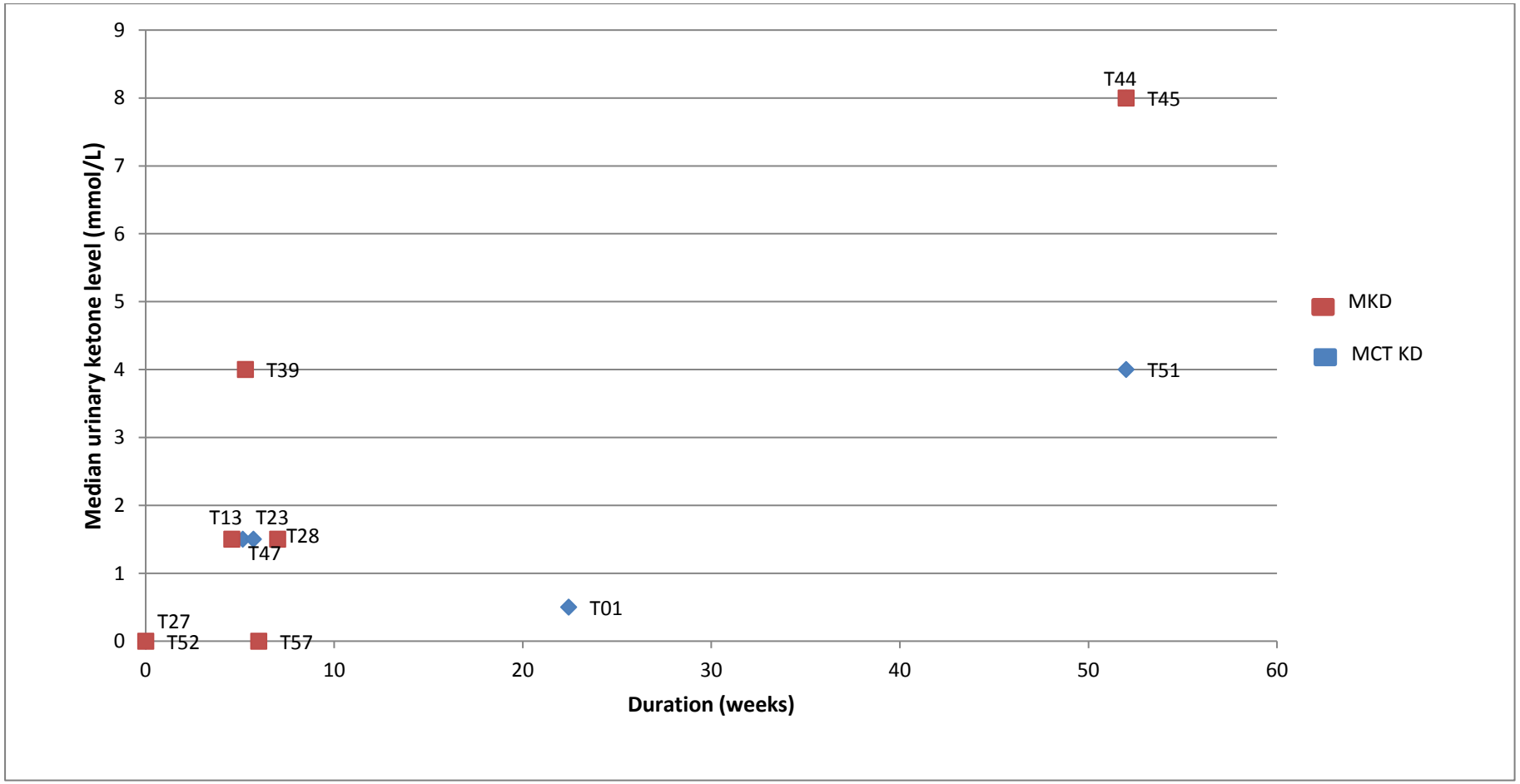
The average level of urinary ketosis for each patient for their duration on diet is presented in figure 4.5. Those who withdrew from the trial reported lower urinary ketone levels than those who retained to month 12.

For those patients who completed six weeks on diet (n=6), the median urinary ketone level was 4mmol/L (0-16mmol/L) for MCT KD group (n=3) and 4mmol/L (0-8mmol/L) for MKD group (n=3). During this time, 79.7% of MCT KD and 79.3% of MKD recordings were within the desired level of ≥4mmol/L.

For those patients who completed three months on diet (n=4), the median urinary ketone level was 4mmol/L (0-16mmol/L) for MCT KD group (n=3) and 8mmol/L (4-8mmol/L) for the MKD patient (n=1). Over the course of three months, 77.4% of MCT KD and 100% of MKD reported recordings were within the desired level of ≥4mmol/L.

For those patients who completed 12 months on diet (n=3), the median urinary ketone level was 4mmol/L (0-16mmol/L) for MCT KD group (n=2) and 8mmol/L (4-8mmol/L) for the MKD patient (n=1). Over the course of 12 months, 96.7% of MCT KD and 100% of MKD reported recordings were within the desired level of ≥4mmol/L.

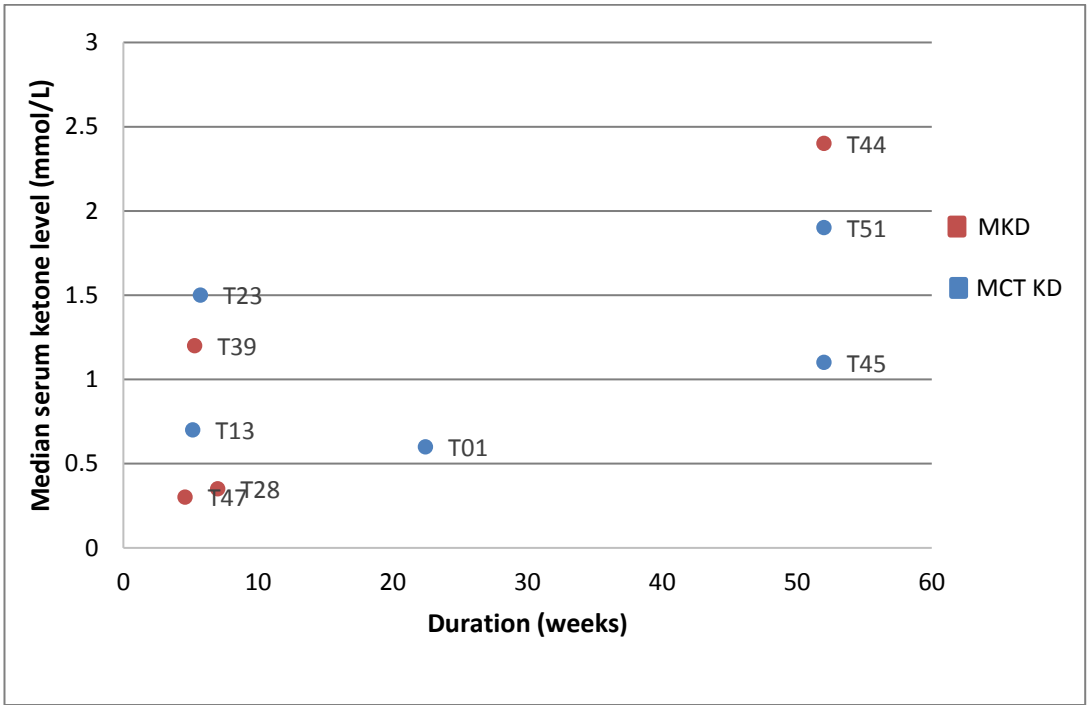
Figure 4.5: Median urinary ketone level for each patient for their duration on diet



Serum ketosis

The average level of serum ketosis for each patient for their duration on diet is presented in figure 4.6. Those who withdrew from the trial early generally reported lower serum ketone levels than those who retained within the trial.

Figure 4.6: Median serum ketone level for each patient for their duration on diet



NB: T51 stopped assessing serum ketones at week six due to tryanophobia, yet continued with diet for 12 months, therefore median data for T51 is based on first six weeks. Remaining patients' data is reflective of their duration on diet.

For those patients who completed six weeks on diet (n=6), the median serum ketone level was 1mmol/L (0.3-4.5mmol/L) for MCT KD group (n=3) and 1.5mmol/L (0.7-3.4mmol/L) for MKD group (n=3). During this time, 29.4% of MCT KD and 35.7% of MKD recordings were within the desired level of ≥2mmol/L.

For those patients who completed three months on diet and monitored serum ketones (n=3)[18], the median serum ketone level was 1mmol/L (0.3-4.5mmol/L) for MCT KD group

[18] Four patients completed three months of KD, however one patient declined to use the serum ketone monitor after week 6 due to trypanophobia.

(n=2) and 2.6mmol/L (1.9-3.4mmol/L) for the MKD patient (n=1). Over the course of three months, 18.1% of MCT KD and 90% of MKD reported recordings were within the desired level of ≥2mmol/L.

For those patients who completed 12 months on diet and monitored serum ketones (n=2), the median serum ketone level was 1.1mmol/L (0.1-4.5mmol/L) for MCT KD patients (n=1) and 2.4mmol/L (1.9-3.4mmol/L) for the MKD patient (n=1). Over the course of 12 months, 36.8% of MCT KD and 97.4% of MKD reported recordings were within the desired level of ≥4mmol/L.

An example of how urinary and serum ketones compared for patients following MCT KD and MKD is illustrated in table 4.11.

Table 4.11: A comparison of urinary and serum ketones at week 6 for patients following MCT KD and MKD

		Macronutrient intake				Median ketone level		
Diet	**Patient trial number**	**Fat (LCT) (%TEI)**	**Fat (MCT) (%TEI)**	**CHO (%TEI)**	**Protein (%TEI)**	**Urinary ketones (mmol/L)**	**Serum ketones (mmol/L)**	**Total duration on diet (weeks)**
MCT KD	T01	46.3	19.8	12.2	19.8	0.5	0.9	22.4
	T45	49.5	31	5.2	13.3	8	3.1	52
MKD	T23	80	NA	3	16.3	1.5	1.5	5.7
	T39	84.9	NA	3.7	10.4	4	1.2	5.3
	T44	75.8	NA	2	21	8	3.4	52

Abbreviations: CHO = carbohydrate; NA= not applicable; %TEI = percentage of total energy intake. NB: Five patients returned completed food diaries and ketone diaries at week six, therefore could be included in analysis. Remaining percentage contribution to total energy intake is derived from fibre and water.

4.4.3.8 Dietetic time required for the dietary interventions

The duration of time associated with clinic visits and non-clinical activities during the first three months and full 12 months are presented in table 4.12 (details of activities undertaken can be found in table 4.7).

Table 4.12: Summary of average dietetic time per participant associated with trial					
Activity	**Diet**	**Consent (hours)**	**Education (hours)**	**Total time: First 3 months (hours)**	**Total time: 12 months (hours)**
Clinical	MCT KD	1.2±0.2 (n=12)	1.3±0.2 (n=12)	6.9±0.2 (n=3)	10.1±0.5 (n=2)
	MKD	1.4±0.1 (n=12)	1.5±0.1 (n=12)	7.5±0 (n=1)	10.5±0 (n=1)
Non-clinical	MCT KD	2.3±1.0 (n=12)	0.8±0.3 (n=12)	6.5±1.0 (n=3)	10.8±1.1 (n=2)
	MKD	2.2±0.5 (n=12)	0.5±0.1 (n=12)	6.6±0 (n=1)	10.1±0 (n=1)

NB: Time presented as mean ± standard deviation.

4.4.3.9 Protocol refinements

There were 24 deviations from protocol during the trial, from seven patients. Deviations occurred due to unreturned food diaries (n=7), unreturned serum ketone diaries (n=7), unreturned urinary ketone diaries (n=3), consultations exceeding schedule or undertaken ahead of schedule (n=1 due to patient commencing diet two weeks after education; n=1 due to patient unable to attend nine month review until month 11; n=1 due to patient attending for review one month ahead of schedule due to clinic facilities), biochemistry derangements (n=1 raised ALT; n=1 raised sodium, both of which were within range on repeat sample), intermittent fasting regimes (n=1) and inclusion of nutritional supplements (n=1).

4.4.3.10 Completeness of data

Seven food diaries (21.1%; n=33), seven urinary ketone diaries (21.1%; n=33) and seven blood ketone diaries (21.1%; n=33) were not returned over the course of the trial. At 12 months, two of the three patients who completed the trial did not return their final food or ketone diaries (n=1 MCT KD, n=1 MKD), which resulted in less than 50% completion rate at 12 months for 'ketosis levels' and 'dietary compliance' outcomes (predefined lower limit criteria for completeness of data was 50%). All remaining outcomes were greater than 75% completed for all time points, meeting the predefined higher limit success criteria, after accounting for withdrawals.

4.4.4 Secondary outcomes: Impact on patients

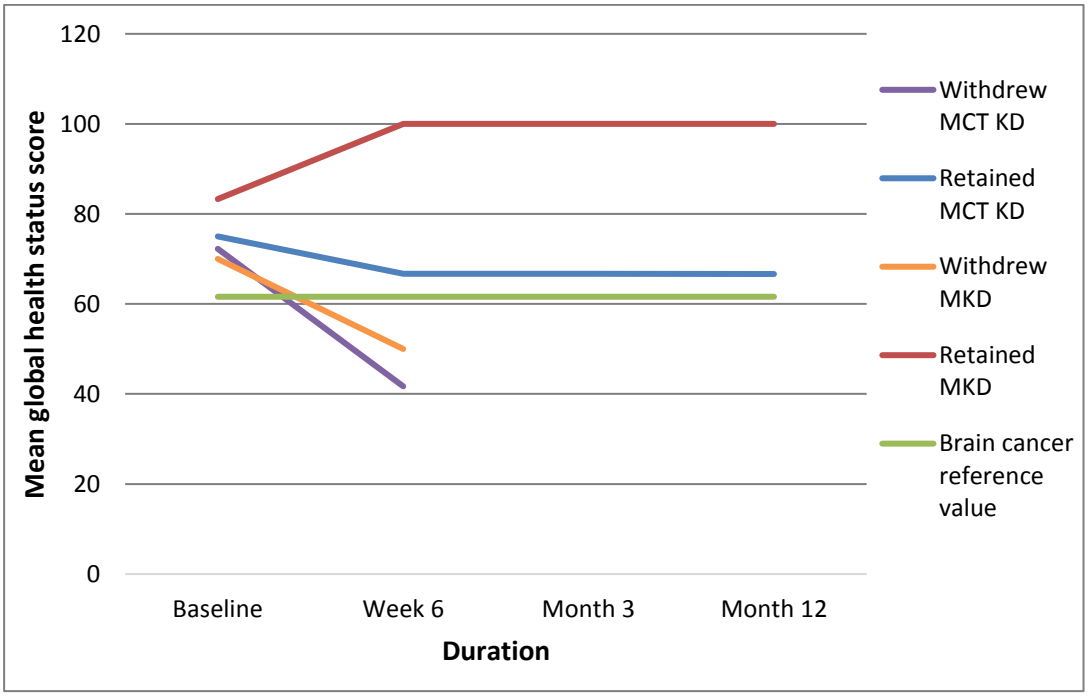
4.4.4.1 Quality of life

The global health status of between both dietary groups for those who withdrew and those who retained in the trial was compared.

At baseline, there was little difference between the global health status of those patients who would go on to withdraw and those who retained within the trial, in either dietary group (withdrew MCT KD 72.2±20.7 [n=3]; retained MCT KD 75±6.8 [n=3]; withdrew MKD 70±13.8 [n=5]; retained MKD 80±0 [n=1]).

At week six, the global health status of those who withdrew reduced, falling below the brain cancer reference value in both MCT KD and MKD (withdrew MCT KD 41.7±0 [n=1]; withdrew MKD 50±0 [n=2]). For those who retained in the trial, global health status improved for the patient following MKD (retained MCT KD week six 66.7±0 [n=3]; retained MCT KD month three 66.7±13.6 [n=3]; retained MCT KD month 12 66.7±8.4 [n=2]; retained MKD 100±0 [n=1] from week six onwards) and reduced for those patients following MCT KD, in both cases global health status remained above the brain cancer reference value (see figure 4.7).

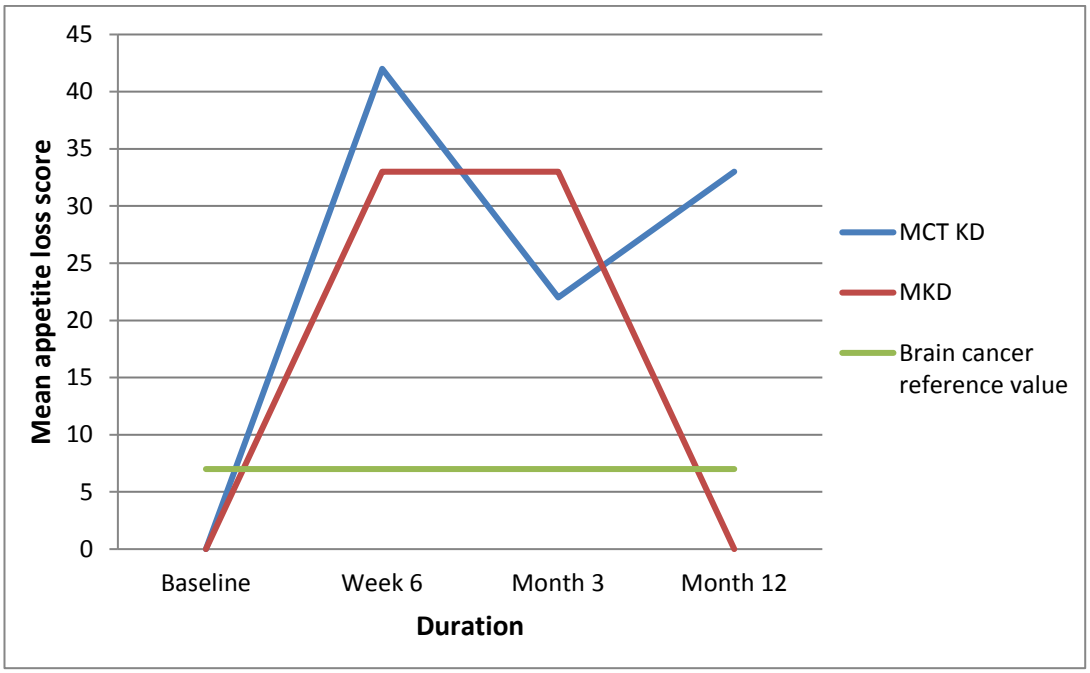
Figure 4.7: Global health status of patients who withdrew and retained in the trial



NB: At baseline withdrew MCT KD n=3, retained MCT KD n=3, withdrew MKD n=5, retained MKD KD n=3; at week six withdrew MCT KD n=1, retained MCT KD n=3, withdrew MKD n=2, retained MKD n=1; at month 3 retained MCT KD n=3, retained MKD n=1; at month 12 retained MCT KD n=2, retained MKD n=1.

Based on patient averages, symptoms (QLQ-C30 and QLQ-BN20 questionnaires) were below the brain cancer reference value with the exception of appetite (QLQ-C30), motor dysfunction (QLQ-BN20), communication deficit (QLQ-BN20) and drowsiness (QLQ-BN20). Of interest for this dietary intervention are appetite and drowsiness. At baseline, appetite was scored zero by all patients (n=12). Appetite worsened during the course of the trial, with appetite loss peaking at week six in both groups (41.7±31.9 MCT KD, n=4; 33.3±33.3 MKD, n=3). At month 12 appetite had resumed baseline levels in the MKD (n=1), with appetite loss worsening in the MCT KD group by month 12 (n=2) (see figure 4.8).

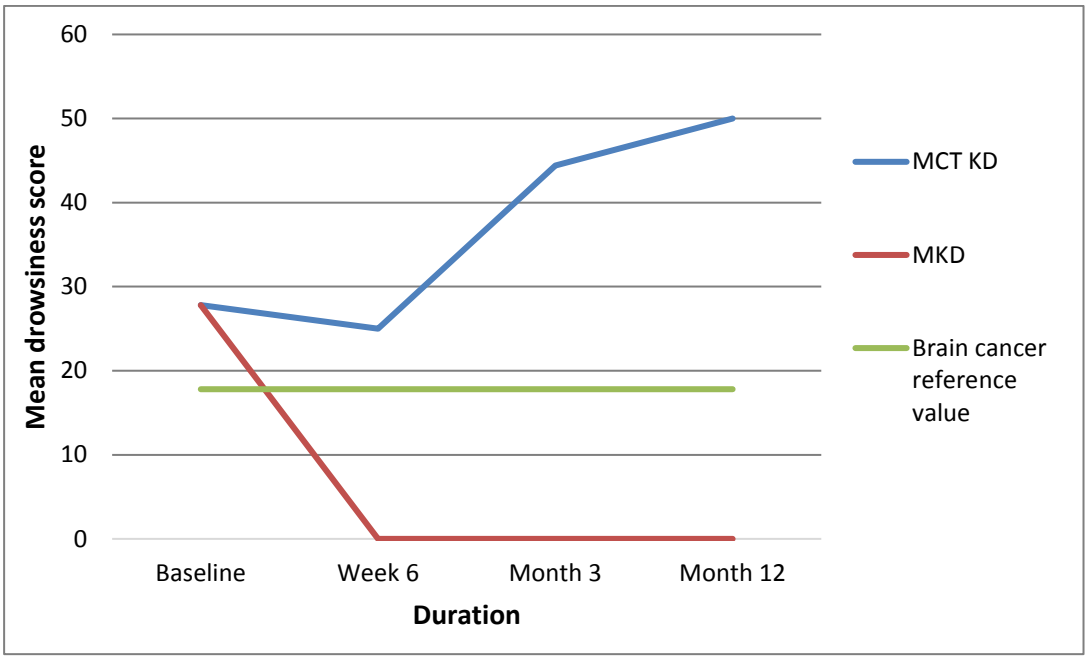
Figure 4.8: Appetite loss reported by patients during trial



NB: At baseline MCT KD n=6, MKD n=6; week six MCT KD n=4, MKD n=3; month three MCT KD n=3, MKD n=1; month 12 MCT KD n=2, MKD n=1.

At baseline, drowsiness was scored above the reference value for both groups (27.8±22.1 MCT KD [n=6]; 27.8±22.1 MKD [n=6]; reference value 17.8). Drowsiness then resolved in the MKD group at week six (score 0 [n=3]) and henceforth for the remainder of the trial (month three and month 12 [n=1]). In the MCT KD group, drowsiness worsened during the course of the trial (week six 25±14.4 [n=4]; month three 44.4±15.7 [n=3]; month 12 50±16.7 [n=2]), see figure 4.9.

Figure 4.9: Drowsiness reported by patients during the trial



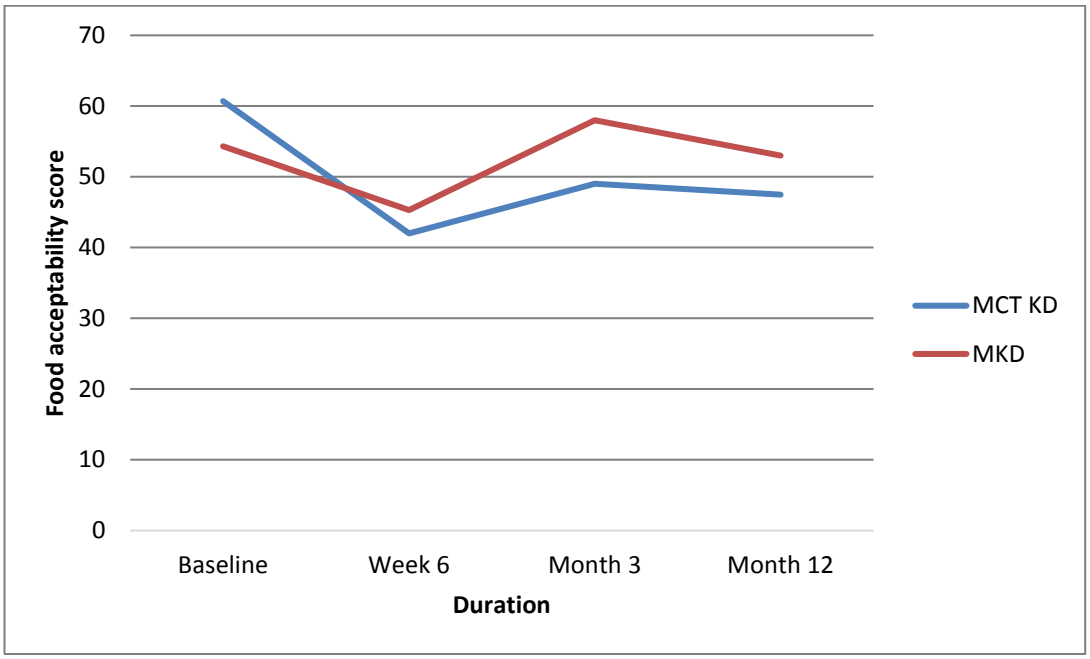
NB: At baseline MCT KD n=6, MKD n=6; week six MCT KD n=4, MKD n=3; month three MCT KD n=3, MKD n=1; month 12 MCT KD n=2, MKD n=1.

4.4.4.2 Food acceptability

Food acceptability reduced from baseline in both groups, with week six receiving the lowest score (baseline MCT KD 60.7±10.5 [n=6]; baseline MKD 54.3±6.2 [n=6]; week six MCT KD 42±8.9 [n=4]; week six MKD 43.5±12.8 [n=4]). Food acceptability then improved between week six and three months (MCT KD 49±2.9 [n=3]; MKD 58 [n=1]), but reduced slightly before the end of the trial (MCT KD 47.5±6.5 [n=2]; MKD 53 [n=1]). Figure 4.10 illustrates food acceptability during the course of the trial.

As more than 50% of patients withdrew before three months, the predefined lower limit success criteria of 50% for food acceptability was achieved.

Figure 4.10: Food acceptability over the course of the trial



NB: At baseline MCT KD n=6, MKD n=6; week six MCT KD n=4, MKD n=4; month three MCT KD n=3, MKD n=1; month 12 MCT KD n=2, MKD n=1.

4.4.4.3 Gastrointestinal side effects

During the first six weeks, the MCT KD group reported four incidences of gastrointestinal side effects and the MKD group two incidences. For the MCT KD group these were diarrhoea (n=1, CTCAE grade 1), nausea (n=1, CTCAE grade 1), vomiting (n=1, CTCAE grade 2), dyspepsia (n=1, CTCAE grade 1) and for the MKD group these were vomiting (n=1, CTCAE grade 1) and a dry mouth (n=1 MKD, CTCAE grade 1).

At month six, one patient (MCT KD) experienced dyspepsia (CTCAE grade 1), constipation (CTCAE grade 1) and diarrhoea (CTCAE grade 1) which led to their withdrawal from the trial. Another patient (MKD) also reported constipation (CTCAE grade 1).

No further gastrointestinal side effects were noted throughout the course of the trial.

4.4.4.4 Changes to biochemical markers

Four adverse events were noted due to deranged biochemical markers; hypokalaemia (n=2, CTCAE grade 1), hypernatremia (n=1, CTCAE grade 1) and hypocalcaemia (n=1, not classified as adjusted calcium >2mmol/L).

Repeat cholesterol data was available for three patients in MCT KD group and one patient in MKD group. Total cholesterol reduced over time in MCT KD group (baseline 6.3mmol/L [4-6.9mmol/L]; month 12 5.6mmol/L [5.3-5.9mmol/L]; n=2) but slightly increased in MKD patient, with this patient experiencing a reduction in LDL and an increase in HDL (baseline total 4.9mmol/L; month 12 total 5.1mmol/L). Total cholesterol to HDL ratio reduced over time in both groups (MCT KD baseline ratio 4 [2-5], month 12 ratio 3.5 [3-4], n=2; MKD baseline 4, month 12 ratio 2, n=1). Changes to cholesterol for both dietary interventions are presented in table 4.13.

Table 4.13: Changes to cholesterol over the duration of the trial

Diet	Measure	Baseline	3 month review	12 month review
MCT KD (n=3)	Total cholesterol (mmol/L)	6.3 (4-6.9)	5.7 (5.3-5.9)	5.6 (5.3-5.9)
	LDL (mmol/L)	3.9 (2-4.5)	3.5 (3.3-3.9)	3.3 (2.7-3.9)
	HDL (mmol/L)	1.7 (1.4-1.7)	1.6 (1.4-1.9)	1.85 (1.6-2.1)
	TG (mmol/L)	1.4 (0.7-2.1)	0.8 (0.7-1.3)	1.05 (0.9-1.2)
	Non-HDL (mmol/L)	4.9 (2.3-5.2)	3.8 (3.7-4.5)	3.75 (3.2-4.3)
	Total: HDL	4 (2-5)	3 (3-4)	3.5 (3-4)
MKD (n=1)	Total cholesterol (mmol/L)	4.9	5	5.1
	LDL (mmol/L)	3.3	2.7	2
	HDL (mmol/L)	1.2	1.6	2.7
	TG (mmol/L)	0.9	1.5	0.9
	Non-HDL (mmol/L)	3.7	3.4	2.4
	Total: HDL	4	3	2

Abbreviations: HDL = high density lipoprotein; LDL = low density lipoprotein; MCT KD = medium chain triglyceride ketogenic diet; MKD = modified ketogenic diet; TG = triglycerides. NB: Baseline data MCT KD n=3, MKD n=1; three month data MCT KD n=3, MKD n=1; 12 month data MCT KD n=2, MKD n=1. Data presented as median (range).

4.4.4.5 Anthropometric changes

Repeat anthropometric measures were available for three patients in the MCT KD group and one patient in MKD group. For the MCT group (n=3), weight, body mass index (BMI), mid arm muscle circumference (MAMC), right hand grip strength (HGS) and waist circumference reduced over time, whilst on average, fat mass was maintained, along with left HGS. Changes were clinically insignificant, with centile ranges being maintained for all measures.

For the one patient following MKD, weight, BMI, MAMC, waist and fat mass reduced over time, whilst HGS was maintained on average. Changes were clinically significant, with BMI reducing from obese to overweight, MAMC reducing from greater than 95th centile to 15th to 25th centile range, waist circumference reducing from high risk to healthy and fat mass reducing from greater than 95th centile to 50th to 75th centile range. Table 4.14 presents changes in anthropometric measures over the duration of the trial.

Table 4.14: Changes in anthropometric measures over the duration of the trial

Diet	Measure	Baseline	3 month review	12 month review
MCT KD	Weight (kg)	88.5 (±11.3)	84.6 (±9.6)	82.3 (±1.3)
	BMI (kg/m2)	29.1 (25.1-33.3)	27.3 (25-31.9)	27.2 (27.1-27.2)
	MAMC (cm)	29.5 (27.1-30.6)	29 (27.1-29.1)	26.6 (24.6-28.6)
	Left HGS (kg)	37 (32.8-47.6)	32 (30.9-44.9)	38.6 (28.2-49)
	Right HGS (kg)	35.9 (34.6-41.8)	32.2 (31.7-40.4)	27.9 (25.9-29.9)
	Waist circumference (cm)	97 (88-116)	92 (88-112.5)	94.8 (88.5-101)
	Fat mass (%)	28.3 (28.3-37.4)	28.7 (22.6-35.3)	28.4 (24.1-32.6)
MKD	Weight (kg)	130.5	97.6	96.6
	BMI (kg/m2)	35.8	31.9	28.9
	MAMC (cm)	33.7	29	28.9
	Left HGS (kg)	43.6	30.9	48.1
	Right HGS (kg)	52.6	32.2	52.4
	Waist circumference (cm)	124	112.5	93
	Fat mass (%)	35.2	35.3	23

Abbreviations: BMI = body mass index; HGS = hand grip strength; MAMC = mid arm muscle circumference; MCT KD = medium chain triglyceride diet; MKD = modified ketogenic diet. NB: Baseline data MCT KD n=3, MKD n=1; three month data MCT KD n=3, MKD n=1; 12 month data MCT KD n=2, MKD n=1. Data presented as median (range).

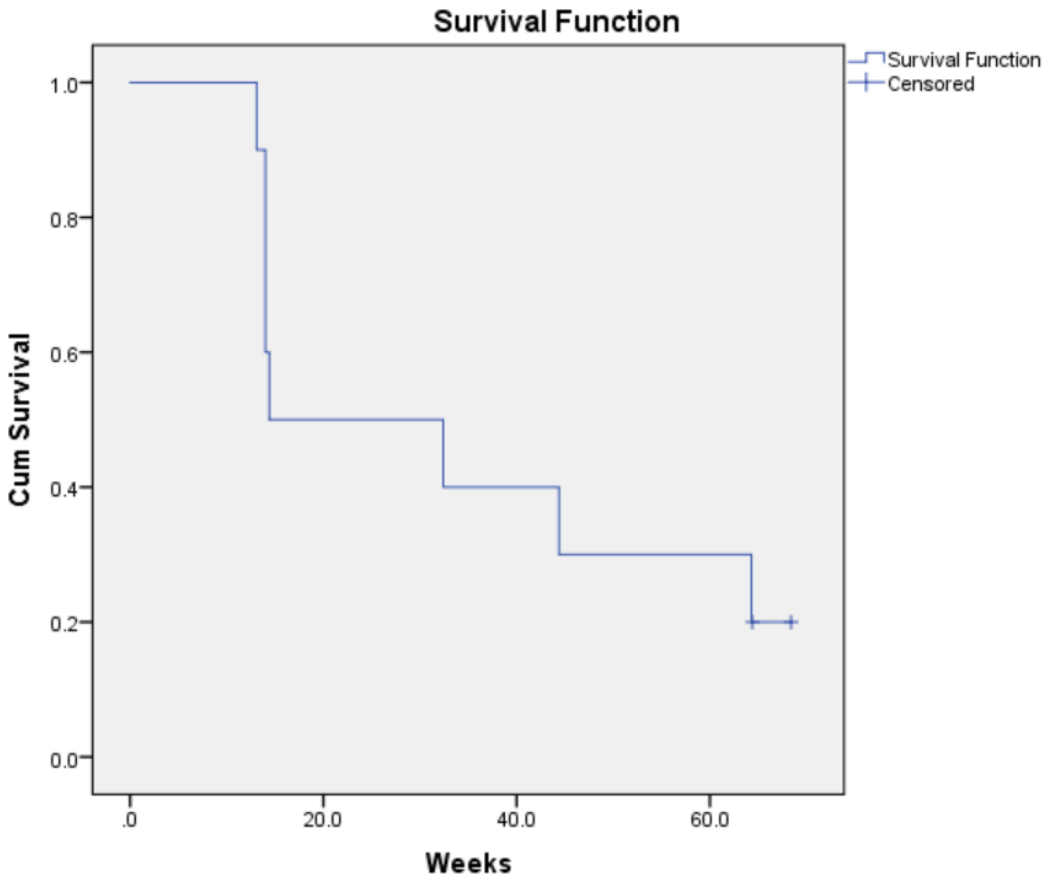
4.4.4.6 Adverse and serious adverse events

Five adverse events and three serious adverse events occurred over the course of the trial. Adverse events were due to hypokalaemia (n=2, CTCAE grade 1), hypernatremia (n=1, CTCAE grade 1), hypocalcaemia (n=1, not classified as adjusted calcium >2mmol/L) and a partial seizure (n=1, CTCAE 1). Serious adverse events were due to post-operative wound infection (n=1, CTCAE grade 3, resulting with withdrawal from trial), seizure (n=1, CTCAE grade 2) and back pain (n=1, CTCAE grade 2), none of which were related to the dietary intervention.

4.4.4.7 Survival analysis

The median time to progression was 14.4 weeks (SE 14.6; 95% CI 0-42.9 weeks). Figure 4.11 illustrates the progression free survival (PFS) of patients who commenced diet (MCT KD n=5; MKD n=5).

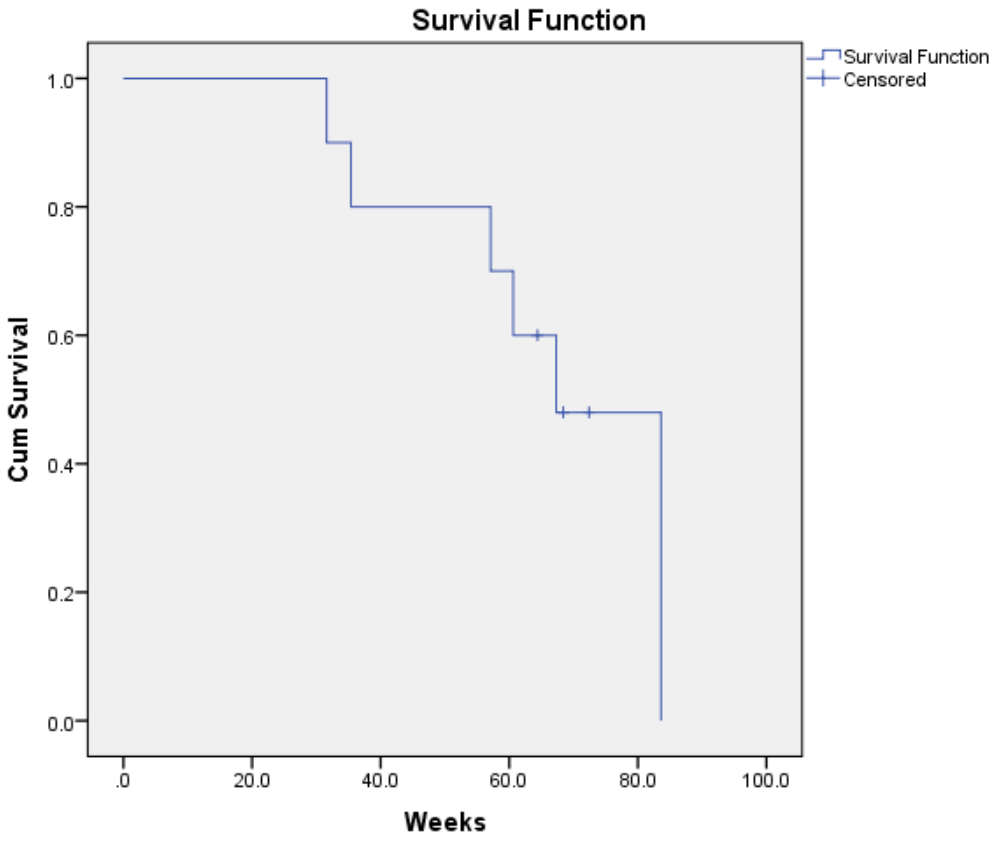
Figure 4.11: Progression free survival



NB: Data censored on 08/MAR/2019 for patients who had not progressed.

Median overall survival was 67.3 weeks (SE 6.2; 95% CI 55-79.6 weeks). Figure 4.12 illustrates the overall survival of patients who commenced diet (MCT KD n=5; MKD n=5).

Figure 4.12: Overall survival



NB: Data censored on 08/MAR/2019 for patients who were alive at time of reporting.

4.5 DISCUSSION

KEATING was designed to investigate if the trial protocol was feasible and explore what impact KD trials would have on patients with GBM, in relation to health and quality of life, comparing two different KDs, in a pragmatic NHS setting. The findings from KEATING will be used to inform the design of future phase III KD trials for GBM.

KEATING experienced problems with dietary retention; of the 12 patients recruited, 10 commenced KD and only four completed the three-month dietary intervention, three of which followed a MCT KD. These retention rates were lower than anticipated, with previous oncology trials reporting trial retention rates of 89% (178), dietary interventions for weight loss reporting dietary retention rates of 50 to 66% at 12 months (209) and previous KD studies for patients with GBM reporting dietary retention rates of 50 to 100% (87,125,126). Yet, patients in these previous KD studies commenced the diet at recurrence or post treatment, rather than at diagnosis, therefore patients' motivations for remaining on diet may differ from those of KEATING and this is explored further in the qualitative study (see chapter 5). The intervention periods of these previous KD studies also differed to KEATING; such as eight weeks (n=2)(126) or to the point of progression (n=20; median five weeks; range three to 13 weeks)(125). Two of the studies also had a limited population (n=2)(87,126). The dietary retention rates for KEATING were lower than our previous NHS scoping service (67% at three months; chapter 3) (169), but both in previous KD studies and the NHS scoping service, patients self-selected to try the diet. These patients may be more motivated than those approached for KEATING, especially if commencing KD following progression. Interestingly, a pilot trial for KD in patients with advanced cancers (breast, ovarian, lung, gastrointestinal), experienced similar dietary retention rates to KEATING (retention rate 31%, n=5 of 16), in a trial which permitted a more liberal KD (70g of carbohydrates per day) and where all food provision was provided (210). Thus, a more flexible dietary approach may not be the simple solution.

Those who withdrew from KEATING did so either after randomisation but prior to commencing the diet (n=2) or after having followed a KD for approximately six weeks (MCT KD median 38 days [36 to 40 days], n=2); MKD 39.5 days [32 to 49 days], n=4), during which time chemoradiotherapy was given to all patients. These results highlight that KDs can be offered alongside chemoradiotherapy for patients with GBM and this is important since data

from animal models suggest that KD is most effective in combination with radiotherapy (79). Nevertheless, future trials may benefit from a shorter intervention period for example, KD delivered for six weeks during chemoradiotherapy only.

Patients who completed the initial three-month intervention stayed on diet for the longer term, with three of the four patients completing the full 12-months. These patients had higher urinary ketone levels compared to those who withdrew, indicating greater dietary compliance amongst those who stayed on diet. Of those who completed the initial three months, three followed MCT KD and one MKD. Our data illustrates patients have a tendency to under consume the supplement, in comparison to paediatric dietary regimes, with MCT accounted for 25% of total energy at three months; a factor to be considered by future clinical and pre-clinical trials as adherence would be required to explore efficacy.

Patients reported reasons for withdrawal to be related to dietary burden and side effects, such as nausea. A recent KD trial for patients with Alzheimer's disease, also highlighted dietary and carer burden to be influential over patient withdrawal (67). As with other oncology trials, withdrawal could also be related to the patients' poor understating of the trial, their motivations and expectations (181,211); factors which are explored further in the qualitative study (see chapter 5).

Initially, recruitment to KEATING was slow, resulting in amendments to the protocol. This included expanding the inclusion criteria to broaden the potential trial population, to offer the possibility of commencing KD during or post treatment rather than prior to treatment commencing, extending the recruitment period by 12 months and embedding a qualitative study. Expanding the inclusion criteria allowed the recruitment of two patients who had undergone biopsy rather than a resection and embedding a qualitative study allowed for the decision-making of patients to be explored, which will be pivotal to the design of future trials (see chapter 5). Patients also benefited from commencing the diet before or during chemoradiotherapy, although no patients commenced the diet post treatment. The extended recruitment period was redundant following an improvement in recruitment rates over the final six months.

The time required for KEATING to embed into clinical services, whereby clinicians acted as gatekeepers for participant involvement (212), was underestimated and may explain the

initial delay to recruitment. Staged recruitment targets, as adopted in other oncology trials (213), would help to alleviate this issue, as would an 'upstream' approach to trial design to alleviate barriers and promote engagement of the clinical team at sites (214). How the trial is initially articulated to patients can also impact recruitment, along with clinician preferences over interventions (215,216). A qualitative study embedded at the point of recruitment would help to explore recruitment practices and patient understanding of the trial and the demands of continued participation. Further research into clinician's opinions of KD trials for patients with GBM would also be beneficial.

Other diet trials have found that shorter dietary/patient information leaflets were beneficial in improving recruitment (102). Whilst we used public and patient involvement (PPI) to design KEATING, we failed to consider how the information sheets and protocol would work in a real-life trial setting (217). The PPI group also involved patients and their relatives who had self-selected to try MKD in the previous scoping service. On reflection, this was perhaps unrepresentative of the overall GBM population from which KEATING would recruit.

KEATING met the recruitment target within the desired timeframe. Despite this, the overall recruitment rate was 28.6%; lower than seen in NIHR HTA funded oncology clinical trials of 50 to 89% (178), with patients declining to participate predominantly due to research involvement, burden of the diet and burden of visits. These barriers are reflective of those usually experienced by cancer trials (174) and trials of complementary therapies (218). The burden of visits could be addressed through utilising linked scheduled clinician appointments between the trial dietitian and oncologist. This would also alleviate the short delay experienced by some patients when commencing the diet due to conflicting appointments. This service was not feasible for KEATING due to dietetic and oncology divisions operating across two separate hospital trusts.

Prior to KEATING little was known about the implementation of KDs for adult patients with GBM. Over the course of the trial, patients who remained on KD, under consumed carbohydrate and over consumed fat. Both MCT KD and MKD groups achieved adequate urinary ketosis (4mmol/L or more)(152), which was maintained over the 12 month trial period. Interestingly, the median serum ketone levels for all but one patient was below the desired level of 2mmol/L over the course of 12 months (219). However, the evidence from which the desired levels are obtained is predominantly based upon animal models, and these

targets may not be achievable in patients, despite good levels of dietary compliance. There is very little evidence in oncology to suggest if these desired levels of ketosis, both urinary and serum, are sufficient to inhibit tumour growth and promote survival, therefore further research is essential. Our findings also highlight that urinary and serum ketones are not comparable, supporting previous literature (220,221). Whilst urinary ketones are cheaper and easier to use, blood ketones offer accuracy; the cost and benefits of which would need to be considered by future trials.

Both diets required a comparable amount of dietetic time over the course of the 12 month trial, approximately 10 hours per patient of face-to-face contact time and 10 hours of non-clinical time, in-keeping with the previous scoping service (chapter 3)(169). Non-clinical tasks included planning of patient menus and recipes (individualised for each patient) cannot be avoided. Some tasks could be delegated to research nurses (anthropometry collection) or administration support (completion of CRFs) which could offer potential cost saving measures for future trial designs.

KEATING is the first KD trial for patients with GBM to assess quality of life by validated means. Those patients who withdrew from the trial at week six, reported quality of life to decrease, with global health status reducing from baseline and falling below the brain cancer reference value in both KD groups. For those patients who retained within KEATING, global health status of those following MCT KD reduced, but not to the extremes of those who withdrew. The global health status of the one patient following the MKD diet improved. The sample of patients who stayed on diet within the trial from which to assess quality of life was small though (n=3), which limits the conclusions that can be drawn. Our findings contradict those of a previous pilot of KD for patients with advanced cancers (breast, ovarian, gastroenterological and lung) in which global health status remained stable, but this advanced cancer pilot did not account for the experiences of those patients who withdrew (dietary retention rate 31%; n=5 of 16)(210). Previous trials with dietary interventions have related withdrawal to a reduction in quality of life (222), yet this was not stated as a reason for withdrawal by patients of KEATING. It could be assumed that dietary burden resulted in a reduction in patients' quality of life, given theoretically this was the primary reason stated for withdrawal and with dietary acceptability reducing over the course of the trial, but this could also be as a result of tumour progression or disease burden (223) and consequently requires further investigation via qualitative means (see chapter 5). Further to global health

status, appetite, motor dysfunction, communication deficit and drowsiness also reduced to below the brain cancer reference value. It is unlikely that changes in communication or motor dysfunction would be related to KD, a reduction in appetite would hinder adherence with the diet. Although paediatric literature finds drowsiness to improve with KD, it is likely that this is due to a reduction in anti-epileptic medication rather than KD itself and also due to a lack of validated measures (53). When considering the patients enrolled in KEATING had neurological tumours, fatigue may occur as a consequence of radiotherapy and neurological injury, as such, drowsiness was to be expected. EORTC QLQC30 and BN20 questionnaires whilst validated, are time consuming to complete and some questions were irrelevant for patients following KDs. It may be beneficial for future KD trials to reduce the length of the questionnaire and therefore patient burden, focusing particularly on global health status; these questions were insightful during KEATING.

Both KDs were found to be safe for use within a GBM population. The MCT KD group experienced more gastrointestinal side effects at initiation than the MKD group, but this was anticipated when using a MCT supplement (56). Gastrointestinal side effects led to the withdrawal of two patients, one within the first six weeks (MKD) and one at six months (MCT KD). Four patients experienced CTCAE grade one electrolyte derangements, all of which resolved by repeat testing. Whilst research into the effect fat has on cholesterol and cardiac health offers contradictory reports, supporting both low fat and high fat diets (224,225), our data offers some preliminary insight into the effect of KDs on cholesterol, with the ratio of total cholesterol to HDL reducing over 12 months and supports previous KD research in adults with epilepsy (89). The results from KEATING contraindicate those of the initial scoping service in which cholesterol increased (169), but this can be explained as patients enrolled in KEATING experienced planned weight loss is due to being overweight or obese at baseline and weight loss known to have a positive impact on cholesterol (226). A larger trial would provide further data on cholesterol and weight loss. Three serious adverse events were noted, none of which were related to KD or the trial. All side effects of KD were less severe than previously noted in paediatric patients (53).

This trial was not powered to assess efficacy or clinical effectiveness on overall or progression free survival. The KEATING population was representative of the usual GBM population in terms of survival (21) and was not biased with respect to known prognostic factors of age, performance status, extent of resection and *MGMT* methylation status. As anticipated, four

patients held *MGMT* methylated genes, two of which also held *IDH-1* and *ATRX* mutations. Both of these patients completed the 12 month intervention and were progression free.

4.5.1 Limitations

This trial has several limitations. As time progressed within the trial, the number of returned patient diaries reduced. This is most noticeable at 12 months, when only one of the three patients returned their diaries, subsequently affecting the 12 month analysis. This is a common problem, given the time commitment required to return diaries. Technology may help to alleviate this issue, through the use of mobile apps, but this could also result in a health inequality. Further PPI work may be beneficial to explore the use of mobile apps and if this would create or alleviate the burden of completing diaries for patients and their relatives. All accounts of dietary intake were also self-reported and at risk of reporter bias (227). However, a review of dietary intake was required to improve ketosis levels and inaccuracies in reporting would be at a personal detriment to the patient. The food acceptability questionnaire, whilst validated for use in vegan diets, was not validated for usw in KDs.

Due to the high withdrawal rates around week six, a post-hoc analysis was introduced to extrapolate further information which may help to explain the withdrawal rates and improve future trial design. Due to poor retention rates only limited analysis could be undertaken at months 3 and 12.

4.5.2 Pilot success

There were five pre-defined criteria for pilot success. Table 4.15 describes the success criteria along with proposed amendments. A phase III KD trial for patients with GBM may be feasible if proposed amendments are implemented, but an internal pilot phase would be recommended. The wider 'keto-oncology' community may also benefit from the proposed amendments given issues with retention in previous trials (210).

Table 4.15: Pilot success and proposed amendments

Outcome	Pre-defined success criteria	Achievement	Amendments
Dietary retention	Dietary retention rate of ≥75% (n=9) at three months	33% (n=4) dietary retention at three months	Shorter intervention period of six weeks to be completed whilst undergoing chemoradiotherapy. Use of an embedded qualitative study to explore patient experience and decision-making (92).
Recruitment	Recruitment rate of ≥75% of target (n=9) achieved within the 12 month recruitment period	100% of recruitment target (n=12) within 12 months	NA
Enrolment of patients	≥75% of patients commenced KD prior to chemoradiotherapy	30% enrolled prior to chemoradiotherapy	KEATING protocol amended to allow patients to commence KD during or post treatment (see section 4.3.1.2). Following which all patients enrolled prior to or within 16 days of treatment commencing. Joint clinics with oncologist to reduce conflicting appointments.
Food acceptability	Diet acceptable to ≥75% of patients at three months	<50% due to withdrawals	Six week KD intervention. Employ a validated questionnaire, if available.
Completeness of data	≥75% of the proposed data collection completed for each end point	>75% completion rate for all outcomes, with the exception of ketone levels and dietary compliance at month 12	Further PPI to investigate if digital solutions for the completion and return of food and ketone diaries would be acceptable to patients.

Key: Achieved success criteria; Did not achieve success criteria.

4.5.3 Implications

The findings of this pilot have several implications for subsequent KD trial designs for patients with GBM. In order to optimise protocol feasibility and patient experience future trials should consider the following suggestions:

4.5.3.1 Suggestions to optimise trial design

- A shorter intervention period of six weeks may be favourable, given the average time to withdrawal during KEATING being 38 days for MCT KD arm and 39.5 days MKD arm. As animal models demonstrate that KD enhances the effects of radiotherapy, it would be advantageous to offer KD during this time within the confines of a trial. During KEATING conflicting clinic appointments between the dietitian and oncologist resulted in a delay in the patient commencing diet of up to 16 days post radiotherapy initiation. Linked appointments, held at one centre, would help to alleviate this issue.
- The trial took time to embed within clinical practice; therefore recruitment figures were initially slow. Future trials should consider a staged, incremental recruitment rate to compensate for this problem. An 'upstream' approach to trial design may improve recruitment practices and clinical team engagement.
- Qualitative studies would be beneficial to gauge clinicians' interest in KD trials for patients with GBM, as this is currently unknown. Furthermore, qualitative studies embedded during the design phase would help to identify challenges unique to the phase III trial, such as randomisation to a control 'no diet' arm, from which strategies to improve the protocol and patient experience could be timely implemented.
- Further PPI would be beneficial to explore if digital media would aid the completion of food and ketone diaries. This PPI should involve patients who have tried KDs before and their relatives/ carers, but also patients to whom KD would be new, a view point which could be essential if dietary retention and trial completion rates are to be improved.

4.5.3.2 Clinical implications

- MCT KD appears to be safe to use in adults with GBM, but leads to more gastrointestinal side effects at initiation than MKD. There may be a role for MCT supplements in adult KDs, but the volume of supplements should be considered. Paediatric levels cannot be tolerated by adults, but volumes equating to 25% of total energy requirements appear acceptable.
- The desired level of ketosis, both urinary and serum, remain unknown for oncology patients following a KD. Future research in this area is essential if efficacy is to be established.
- Further research is required before KDs can be implemented in neuro-oncology. KDs are currently not recommended by NICE (166).

4.6 CONCLUSION

Recruitment of patients with GBM to a KD trial is possible. To assess efficacy in a clinical trial, a six week intervention period is proposed. Further qualitative studies embedded within these clinical trials are essential to optimise trial design and patient experience. A phase III trial would benefit from an internal pilot to further test the recommendations derived from KEATING.

4.7 Acknowledgements

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CHAPTER 5

DECISION-MAKING OF PATIENTS WITH GLIOBLASTOMA INVITED TO JOIN A PILOT TRIAL OF KETOGENIC DIETS (KEATING): QUALITATIVE STUDY

5.1 CHAPTER OVERVIEW

Following on from the quantitative findings of KEATING reported in chapter 4, this chapter presents a qualitative exploration of patients' perspectives of their decision-making when invited to participate in KEATING. This study was conceived following recognition that KEATING faced challenges with recruitment. Eight months in to the twelve month recruitment period, with an uptake of less than 30%, KEATING was falling behind on recruitment targets. It was therefore deemed crucial to understand why some patients were deciding to participate, whereas others were deciding to decline involvement. Whilst there is an abundance of literature regarding the decision-making of patients involved in drug trials, there is little evidence on the decision-making of terminal oncology populations in feasibility or early stage clinical trials, as noted in the narrative review to follow, especially for dietary interventions. To our knowledge, patients' views on ketogenic diets (KDs) generally have also not been explored by qualitative means, either within the context of a trial or within clinical practice. Following discussions with the Trial Management Group (TMG) and Trial Steering Committee (TSC) of KEATING, a pragmatic, solution-based decision was made to embed a qualitative study within KEATING.

This chapter begins by introducing decision-making in healthcare settings, followed by a narrative review of the qualitative literature relating to the decision-making of patients with advanced cancer, when faced with early phase clinical trial participation. The chapter then progresses to present the methodology adopted by this embedded qualitative study and the analysis of data and defined themes, prior to discussing the results in the context of the wider literature. The chapter concludes with recommendations for future KD trials for patients with GBM. The Standards for Reporting Qualitative Research (SRQR) was utilised throughout this chapter (228).

The study protocol (version 4, 20/DEC/2017) can be found in appendix H, along with associated documentation relevant to the qualitative aspects (appendix N).

5.2 INTRODUCTION

5.2.1 Decision-making in healthcare

Shared decision-making, between a patient and healthcare professional, is the pinnacle of patient centred care (229,230). This approach is tailored to individual patients' needs, and allows patients to weigh up the risks and benefits of a treatment or intervention whilst taking account of their personal values, thus enabling them to make an informed decision about the care they are receiving in relation to their health (230,231).

Shared decision-making is widely accepted throughout healthcare and is recommended by the National Health Service (NHS; (232)). However, whilst this practice is considered the 'gold standard' in relation to healthcare decisions, the process of decision-making in health is complex and can vary according to the nature and type of decision being made (233). For most patients, the decision goes beyond cognitive processes, such as weighing up the risks and benefits, to include factors such as emotion, feelings of fear or hope (234). These emotions can have a greater influence on decision-making depending upon the severity of the disease. Some patients may prefer others (healthcare professional or relative) to assist with the decision-making, taking a relational approach to autonomy (235). Thus, the extent of the role the patient wishes to have and the role of the healthcare professional can vary on an individual basis.

The extent to which the patient wishes to be involved in the decision may also change over time and can be dependent upon their condition (231). For patients with advanced cancers, initially prolonging life can be the patient's main focus when deciding about treatment options; with quality of life becoming more important than prolonging life, as the disease progresses (231). This occurs at a time when patients seek increased control over the decisions regarding their care, becoming more active in the decision-making process (231).

5.2.2 Decision-making in clinical trials

One area of particular importance in which patients are required to make decisions relates to participation in clinical trials. Clinicians seek informed consent from patients when they are enrolling into a clinical trial. When considering trial involvement, it is presumed patients will enter into a deliberation phase of decision-making, whereby they seek and process information relevant to their decision, assess the sufficiency of their knowledge, consider counterarguments to their decision, account for how emotions will influence their decision, consider their personal preferences in the construction of their arguments to support their

decision and consider their own readiness to make a choice (236). In practice, decision-making for clinical trial involvement is often more complex, in part due to the lack of optimal consent procedures and insufficient decision-making support, which may result in patients having a poor understanding of the clinical trial (229).

Recent research attention has been paid to the importance of understanding patients' decision-making with regards to clinical trial participation, particularly in oncology, so as to optimise both informed consent to trials and the patient experience. Several qualitative studies have been successfully embedded into diet-oncology trials for breast and prostate cancers with varying aims such as investigating barriers to recruitment and exploring patients' views on prostate cancer and diet (101–107). Whilst these studies are of interest methodologically, the findings are unlikely to be transferable to patients with advanced cancers, such as glioblastoma (GBM). Whilst 78% of patients with breast cancers (237) and 84% of patients with prostate cancers survive beyond 10 years (238), only 5% of patients with GBM survive beyond 5 years (239). Moreover, trials of interventions aimed at providing remission are readily available for patients with breast and prostate cancers, but for patients with advanced cancers such as GBM, early phase clinical trials investigating safety and toxicity of treatments are often the only clinical trials available. Therefore, the offer to join a trial is may have a different meaning for patients with GBM, compared to those with breast or prostate cancers. In order to adequately support patients with advanced cancer in making decisions about participation in early phase clinical trials, a better understanding of their decision-making processes is vital.

5.2.3 Decision-making of patients with advanced cancers regarding participation in early phase clinical trials: a narrative review

The following narrative literature review explores the qualitative literature relating to the decision-making of patients with advanced cancers regarding participation in early phase clinical trials (see appendix P for narrative review methodology and appendix Q for search strategy (240)). Five publications, from four studies, were identified for inclusion in this narrative review (241–245). Each is briefly discussed below, followed by a summary of their strengths and limitations, and collective findings.

The first embedded qualitative study exploring decision-making processes of patients with advanced and metastatic cancers was undertaken in the late 1990s (241). This study found patients did not follow theoretical decision-making pathways, such as those outlined previously (236), but instead made an instantaneous decision about participation which was

based upon intuition. Patients did not report considering the advantages and disadvantages of participating, or deliberating their decision. Whilst participants described seeking further information about the trial, and valued being given time to consolidate their decision, these factors did not affect the participants' initial decision. Later emotional factors, such as hope for a cure, prolongation of life, reducing fear of death were considered, reducing anticipated decisional regret. Having small children or a partner also provided motivation to participate. Despite the instantaneous initial decision and contrast with theoretical models of decision-making (236), most participants described being happy with their decision on reflection. Those who did experienced greater side effects from the chemotherapy intervention were unhappy within the trial (241).

Whilst this study was the first of its kind and provided insight into the decision-making processes of patients with advanced cancer regarding trial participation, there are several limitations which may restrict the generalisability of its findings. First, despite data being collected on contextual factors such as education, employment and religion, the influence of this on the decisions and opinions of participants was not taken into account. Second, patients who declined to participate in the clinical trial were under-represented in the qualitative sample (n=13 consented; n=1 declined). This is an important omission because, in some cases, the perspectives of those who declined can be invaluable to understand how the rationale for their decision and the processes behind their decision may differ from those of consenting participants (173). In relation to recruitment, understanding the thoughts and decisions of those who decline and those who withdraw are essential to improve trial design and minimise health inequalities relating to health literacy barriers (246–249). Finally, the interviews were conducted at the trial hospital sites by a research nurse, which may have caused response bias. Strengths to the study included interviews being undertaken longitudinally, to gain depth about the participants' decision and how this may change over time, and were analysed by four healthcare professionals, one of whom was a psychologist, aiding triangulation and reducing reporter bias.

Madsen et al., (2007) were the next research group to explore the attitudes of advanced breast and ovarian cancer patients regarding participation in early phase clinical trials (242,243). The semi structured interview study used grounded theory, and included patients who did and did not take part in clinical trials. In contrast to Huizinga et al., (1999) (241), all patients, both those who consented and those who declined, reported giving full consideration to participation, yet many reported lacking sufficient knowledge to make educated choices (243). Their decision processes were consistent with Gillies et al. (2014)

decision-making theory in that participants weighed personal advantages against the risks and disadvantages of participation. In keeping with the findings of Huizinga et al. (1999), patients made their decision based on their personal interests, primarily in a non-altruistic manner. Yet, on later reflection, those who participated partially considered their decision to be due to a moral obligation. A perceived lack of clinical equipoise between the intervention and control arms and a lack of understanding about randomisation also influenced the patients' decisions. Those who participated perceived the intervention arm to be of superior benefit, whilst those who declined considered the intervention arm to be of greater risk, resulting in fear due to the 'chance' of being allocated to the intervention. The random allocation of trial groups potentially removed the aspect of 'hope' which the intervention provided to those who wished to participate. Whilst all participants were positive in attitude towards clinical trials, those who declined, when faced with the personal decision to participate, were more cautious in their approach than those who consented, which influenced their decision to refuse. Most patients were confident with the clinician making the decision for them, further indicating the importance of relational autonomy in this patient group (235).

Whilst this study included both participants who consented and those who declined, the sample was female dominant due to the nature of the diseases in question, advanced breast and ovarian cancers. Unlike Huizinga et al., (1999), interviews were conducted at one time point, rather than longitudinally, six months after the patients' initial decisions. Therefore, it is unknown if the views expressed by patients were a true reflection of their decision-making at the time of the event or if they could have been influenced by participating in the study or the passing of time. Due to the decision of the ethics panel, moral obligation could not be explored and those without a treatment response could not be interviewed, consequently their experiences and opinions remain unknown. However, interviews were carried out at the patients' own homes, which reduced interviewer bias. The sample was also fairly balanced between those who consented and those who declined.

A subsequent qualitative, cross sectional, interview study exploring the decision-making processes of advanced haematological and melanoma cancers patients participating in phase I clinical trials was undertaken by Godskesen et al. (2013) (244). Participants reported the main reason for participating in a phase I trial as being 'renewed hope'. Despite receiving written and oral information about the study, no participant could recall the purpose of the study. As this study included phase I clinical trials only, no control arms were present. Patients, therefore, perceived the introduction of trial participation by the clinician as a

positive experience, as they believed the clinician would not present an ineffective treatment option. Like Huizinga et al. (1999), patients recalled making an instant decision to participate, with many not reading the consent form before signing it. This contrasts with the decision-making processes reported by Madsen et al. (2007), and points to difficulties in obtaining informed consent in this study. Patients' instantaneous decision to participate was influenced by their failed treatment history and the advanced nature of their cancer, indicating an emotional aspect to their decision-making. Some participants shared their decision with a family member, seeking validation and support, whilst others independently decided whether or not to participate. For some, trial participation provided an aspect of hope and optimism for a cure, with many participants disproportionately over anticipating the likely outcome of survival or likely success of a phase I trial, and most considering hospice care to be their next option if the trial failed. Some also believed this optimism would provide therapeutic benefits. As with previous studies (241,242), most participated for personal benefit, rather than for altruistic reasons.

This study had several limitations. The sample demographics for this study are unknown, hence it is difficult to interpreted if the study is influenced by gender bias as with those previously discussed (241–243). However the oncological conditions applicable to this study do affect both male and female populations. An element of recall bias may be present - two of the fourteen participants completed the phase I trial four months prior to being interviewed, whilst the remainder completed the interview whilst still enrolled on a trial. The duration between consenting to the trial and being interviewed was not reported. The interviews took place at patients' referring hospitals, which could result in reporting bias, and interview duration was short in some cases (mean 30 minutes, range 15-55 minutes), which may affect the quality, depth and richness of the data. The study did not include any patients who declined to participate in phase I trials, therefore their views and decision-making processes remain unknown. Furthermore, only participants of the trial were interviewed, thus the views of their family members, and the potential influence of these on patients' decision-making, were not fully explored. Nevertheless, all interview material was discussed between five authors, which provided a means of triangulation and increased credibility.

More recently, an embedded, qualitative, semi-structured, interview study using a grounded theory approach was undertaken to identify the motivations and barriers of patients with advanced stage IV breast cancer and their decision-making processes for participating in phase I clinical trials (245). As with previous studies, the purpose of the phase I studies (i.e. investigating toxicity and safety rather than efficacy) was not well-understood by the

majority. Many participants over-exaggerated the possible health benefits afforded by participation, with many reporting the study to be investigating efficacy. Yet, some participants did note that efficacy was related to their own personal agenda and optimism, and not the true purpose of the study, illustrating issues with understanding and their appreciation of that knowledge (250). The clinician's recommendation and participants' trust in the clinician were the main influence over their decision to participate, as previously reflected in other studies (242,243). Some participants were influenced by relatives with pre-existing healthcare knowledge. Face-to-face consultations and trial information sheets were the only resources participants used to make their decision, which contrasts with models of decision-making, and with the findings of other studies (236,241,242). Some participants described dependants, such as young children, as a motivation for their decision to participate, which is consistent with Huizinga et al. (241). Several participants considered receiving cancer treatments as a 'fight' for their life, and saw the addition of a phase I treatment alongside their standard care as an additional benefit. They thus described viewing the trial as providing access to better treatment. The option of receiving hospice care instead of a phase I trial was not considered by this population. Most were able to recall some risks associated with the trial, but for most these risks did not appear to influence their decision. In agreement with a previous study (244), hope appeared to be a key influence over their decision to participate; participants spoke about the trial offering hope for a cure or preventing progression, and many viewed hope alone as having a positive influence over their health and coping with cancer, despite their understanding of their prognosis.

As with other studies, only those who participated in the trials were interviewed, and therefore the views of those who declined to participate remain unknown. Participants were interviewed after their decision to participate, but the time between the consent procedure and the interview was not specified by the authors, raising the possibility of recall bias. However, all interviews were conducted by a researcher independent to the trial team and participants' care, which may potentially have reduced reporter bias and researcher influence over the data. Two coders also independently coded the data (245), offering the benefits of data triangulation and improving the validity of their results.

Summary of findings

Despite a comprehensive literature search, few studies were identified which explored the decision-making processes of patients with advanced cancers regarding participation in early phase clinical trials. Narrative synthesis of these studies provides some clues as to factors

which may play an important role in decision-making in this context. All studies present optimism through hope as influencing participants' decisions. Some theorists consider this optimism bias, a desire for an extraordinary outcome compared to the average patient, to compromise informed consent (251). Despite this, in later studies, the authors present optimism as a coping strategy for dealing with a cancer diagnosis, thus not invalidating informed consent (252), which supports the theories of others (253). Most studies also present emotionally-laden situations as leading to an instantaneous decision about participation (241,244), rather than a decision which is necessarily constructive and considered (242). Despite this, findings from the above mentioned studies suggest that participants do not generally regret their decision to participate, and increased time to reflect upon their decision does not appear to alter their initial decision. Data also suggest that patients' decisions are often personal and made in a non-altruistic nature, although point to the importance of family influences on decision-making, thus suggesting the role of conditional altruism in influencing participants' decisions (254). The role of relational autonomy through trust in the clinician was also apparent and, in certain instances, may influence participants' understanding of equipoise.

Although informative, the literature exploring decision-making processes for early phase clinical trials in oncological conditions has several limitations which make generalisability to GBM populations difficult. First, it is based predominantly on the accounts of females with non-neurological tumours, hence may not directly relatable to the decision-making of patients with GBM, particularly given that patients with GBM may also experience cognitive decline which could influence their decision-making processes. However, all patients' conditions were advanced in nature with treatment offered for palliative purposes, which is a similar treatment and prognostic position to GBM care. Second, although all included studies explored patients' initial decisions to participate, there is no literature exploring how or if this decision changes over time for patients with advanced cancer, despite knowing patients' decision-making in relation to their healthcare changes as the disease progresses (231). There is also very little evidence exploring the decisions of patients who declined to participate in early phase advanced cancer trials or exploring the roles of relatives in the decision-making of patients, therefore their views remain unknown. In order to optimise informed consent and patient experience in subsequent KD trials, we need to know more about the experiences of patients with GBM and how they make decisions.

5.2.4 Aims and objectives

This study aimed to explore patients' and their significant others' perspectives of their decision-making when invited to participate in KEATING.

Specific objectives were to:

- Understand patients' perspectives of their decision-making participation in KEATING.
- Explore the views of relatives and their influence on patients' decision-making.
- Explore patients' ongoing decision to participate in the intervention once recruited.
- Design bespoke strategies to optimise the decision-making of future patients with GBM invited to participate in KD trials.

5.3 METHODOLOGY

5.3.1 Study design

A qualitative study embedded into KEATING eight months into the initial recruitment period due to difficulties with recruitment and dietary retention of patients. The study involved semi-structured interviews with patients and their relatives.

5.3.2 Ethical and study approvals

Ethical approval was granted by the North West - Greater Manchester West Research Ethics on 20th December 2017 (protocol amendment 2), along with Sponsor and WCFT approvals.

5.3.3 Presentation of KEATING to patients

To provide context to the embedded qualitative study, a recap of the approach taken to recruit potential patients will be briefly described (for full details see chapter 4).

Following a histological diagnosis of GBM, a member of the neurosurgical/ oncology team at the hospital Trust briefly discussed KEATING with the patient. If s/he was interested, the trial dietitian provided further details of the KD and the trial, supported by written information. After providing consent, patients were randomised to follow either a medium chain triglyceride ketogenic diet (MCT KD) or a modified ketogenic diet (MKD) for three months (primary end point) (for details of the interventions see table 5.1). All patients received dietary education. This consisted of recipes, meal plans, KD information sheets on foods to

consume or avoid and the home monitoring required, such as urinary and blood ketones (high ketones being associated with compliance and efficacy in animal models). Patients also had regular dietetic contact throughout the trial. Outcomes included protocol feasibility (estimation of retention and recruitment rates for a phase III clinical trial, dietary adjustments required to achieve ketosis, dietary compliance, ketosis levels) and the impact on patients (quality of life, dietary acceptability, gastrointestinal side effects, anthropometric and biochemistry changes).

For KEATING, 57 patients were approached to take part between March 2017 and February 2018. Of these, 15 were excluded, 30 declined and 12 consented. Six were randomised to MCT KD and six to MKD. Of these, three completed the three month dietary intervention MCT KD arm and one in the MKD arm.

Table 5.1: Comparison of MCT KD and MKD dietary interventions

Intervention	MCT KD	MKD
Macronutrients	**10%** carbohydrate **75%** fat (**30% of which from MCT nutritional products**) **15%** protein	**5%** carbohydrate **80%** fat **15%** protein
Example meal	Bacon x 2, eggs x2 scrambled with **2 dsp double cream**, ½ avocado**, 1 ½ tomatoes**, **½ slice low carb bread**, handful spinach and **100ml Betaquik MCT nutritional product**	Bacon x 2, eggs x2 scrambled with **4 dsp double cream**, ½ avocado, handful spinach and **mushrooms fried in 1 tablespoon oil**
Requirements of patients	Urinary ketones twice daily Blood glucose and ketones weekly Intermittent food diaries Dietitian appointments	Urinary ketones twice daily Blood glucose and ketones weekly Intermittent food diaries Dietitian appointments

NB: Bold text highlights differences between the dietary interventions. MCT nutritional products provided in the form of Betaquik (Vitaflo International Ltd). Ketones are monitored Further details of the interventions and monitoring can be found in a previous publication (255). Abbreviations: dsp = dessert spoon; MCT KD = medium chain triglyceride ketogenic diet; MKD = modified ketogenic diet.

5.3.4 Participants

Eligibility criteria for qualitative study:

1. Patient interviews
    a) Patient approached to participate in KEATING (see chapter 4 for KEATING eligibility criteria).
    b) Capacity to give informed consent.
2. Relative interviews
    a) A relative of a patient approached to participate in KEATING.
    b) Capacity to give informed consent.

As the qualitative study was introduced eight months after KEATING had commenced, patients approached for KEATING from this point onwards were eligible for the qualitative study or if they had been approached to participate in KEATING three months prior to the qualitative study commencing.

Patients could be interviewed for their sole experience, whilst relatives were only invited to participate as a dyad with the patient.

5.3.5 Sampling

Participants for the qualitative study were a purposively sampled sub-set of patients who had been approached to participate in KEATING, and their relatives (256,257). Sampling was informed by review of screening logs maintained as part of KEATING and aimed to include those who consented to KEATING, those who declined KEATING, those randomised to MCT KD and those randomised to MKD. The principles of informed consent mean that when patients withdraw or decline from trials they are not obliged to give a reason for their decision if they do not wish to. However, this qualitative study invited patients to participate even if they declined or withdrew from KEATING as they may have wished to convey their perspectives and it is important to understand the experience of both those who consent and those who decline.

Adequate sample size was determined using the 'information power' concept (258,259).

5.3.6 Semi structured interviews

Primary data was generated by the researcher through semi-structured interviews which explored the patients' perceptions of their decision-making after being invited to participate

in KEATING. Interviews were selected over focus groups to provide a depth of information about participant's and their relative's decision making, rather than the breadth offered by a group dynamic (92). Furthermore, interviews allowed for discussion of sensitive topics given the patient's prognosis. Participants were also dispersed geographically and interviews were to be completed within set timescales (260). Interviews were conversational and patient-centred, using open-ended questions. Questions were adapted depending upon if the patient consented or declined to participate. As the researcher had a dual role (dietitian and qualitative researcher), the interviews were conducted in a gentle, sensitive and non-judging manner, to make the experience as comfortable as possible for patients.

The interviews were topic guided (for patient, relative and dyad topic guides see appendix R) and iterative, allowing for the development of interviews over time. The topic guide was informed by published literature and incorporated the study objectives. It was devised by two members of the research team, one of who had extensive qualitative experience. Any questions in which the patient or relative felt obliged to justify their decision were avoided. Patients and relatives were free to decline to answer any questions or terminate the interview at any point. An overview of the topic guide can be found in table 5.2.

Interviews took place in the patients' own home, workplace, by telephone or at WCFT depending on the patient or relatives preference. Patient and relative interviews were usually undertaken separately, but could be undertaken jointly at their request.

Table 5.2: Overview of the topic guide		
Section	Example questions	Example prompts
Study information and recruitment process	Who initially told you about the study?	Can you tell me about the run up to the study? Can you remember when you were first diagnosed? Is there anything would you change about how you were approached? When would you prefer to be approached? Who would you prefer to approach you about the study?
	What is your understanding of the reason why the study is being done?	What is your understanding of what the study aimed to investigate? Are you able to tell me a bit about what this involves for patients?
	We posted an information sheet to you about the study (demonstration sheet provided). What are your views on it?	Did you find the wording and layout suitable? Is there anything that you would change? Were any parts helpful? Did you have any questions after reading the leaflet?
Decision-making	Before making your decision about taking part did you seek information from anywhere else?	Did you discuss your involvement in the study with your family or friends? Did you discuss the study with a doctor or nurse?
	Can you tell me about how you came to your decision to take part/not take part in the study?	When did the decision start to form in your mind? How do you usually make decisions (gut reaction or evidence based/ informed decision)? How certain were you with your decision? How confident were you with your decision?
	Are there any potential changes that could be made to alter your opinion?	Any changes to the study design? Changes to how you are told about the study and what it involves?
	When thinking about the treatment you have received, is there any time when you think starting the diet would be most appropriate?	This could be not at all, before/after surgery, before/ during/ after radiotherapy or before/ during or after chemotherapy or after all treatment has finished. Can you tell me a bit more about that?
	Did you consider any other studies or treatments?	Other studies that may be open to you locally or nationally? Have you taken part in research previously? Would you take part in potential future studies? Have you looked into any other diets or nutritional supplements?
	If you had the chance to be involved in the study again would you make the same decision?	If changed decision why is that?
Experience of KEATING (KEATING participants only)	What did you think when you were told about your allocated diet?	Did you have any worries or expectations? Do you have any particular views on being randomised to one diet or the other?
	What has your experience of the KEATING study been so far?	Has your experience influenced your views on research? Do you have any tips for a similar study in the future? Has any part been particularly burdensome? Have there been times when the diet has been more difficult to follow? Have there been times when the diet has been easier to follow?
Conclusion	Is there anything else you would like to talk about that we haven't covered? Do you have any questions for me? Thank you for taking the time to talk to me.	Can you tell me more about that? What is your understanding of that?

5.3.7 Data management and transcription

All interviews were audio recorded and transferred onto a password protected file held on University of Liverpool Active DataStore for analysis. All audio recordings were transcribed verbatim, checked and anonymised for analysis.

5.3.8 Data analysis

Analysis drew on the Braun and Clarke thematic approach to identify patterns of meaning within the data (261), with KM initially familiarising herself with the data, then generating initial codes, searching for themes, reviewing themes, defining and naming themes and the careful placement of theory prior to producing a report. KM lead a process of iterating between the developing analysis and new data (familiarisation,). Other members of the qualitative study team (BY and GC) read a sub-set of transcripts and developed the analysis by periodic discussion. Qualitative researcher BY is an academic psychologist with extensive experience of embedded qualitative studies within trials, and GC is a clinical psychologist specialising in oncology and has experience in nested qualitative studies and research exploring patient perspective. An adequate sample was obtained drawing on the concept of 'information power' (258).

Analysis did not take accounts only at face value; rather the approach was interpretive and considered both latent and manifested aspects of the data (e.g. what we could learn from the way that patients and relatives talked as well as the explicit content). Context to the interviews was provided through the use of field notes taken by the researcher at the time of interview. The design, conduct and analysis of the qualitative study was informed by procedures that support quality in qualitative research including systematic data coding, triangulation and exceptional case analysis (262,263). The Index of Multiple Deprivation (IMD) for England and for Wales, qualitative studies of deprived areas, were also consulted to provide context to the results (264,265). Analysis was assisted by qualitative analysis software (NVivo 11). Results were fed back to the KEATING TSC.

5.3.9 Philosophical underpinnings

The orientation of this qualitative study was both inductive and deductive, with the study being designed pragmatically to explore the decision-making processes of patients invited to participate in KEATING. To understand patients' decision-making (the phenomenon in

question), a subjectivism/ constructivism ontological approach was taken,[19] understanding patients' decisions through their perceptions and interpretations of events. Their interviews were then analysed interpretatively, constructing meaning and interpretations, from both latent and manifested aspects of the verbal accounts (266,267).

5.3.10 Reflexivity

Reflectivity is important in qualitative research as it allows the researcher to contemplate how their beliefs, background, attitude and values affect the research (268). A personal reflection attempts to limit researcher subjectivity to reduce potential bias in the collection, analysis and interpretation of data, thus improving trustworthiness and validity of the study (269–271).

Personal reflection

I am a white-British, married female, residing in the north west of England. I am a registered dietitian and have worked within the NHS for the past ten years, the last five of which I have specialised in neurological conditions, with expertise in KDs. I obtained qualitative research skills through University of Liverpool modules and two Social Research Association (SRA) courses.

For KEATING I held a dual role; i) trial dietitian and ii) qualitative researcher. I immediately appreciated the bias this may present, given I would be recruiting patients, providing dietary education and support, and managing the day to day running of the trial, whilst interviewing patients and relatives about their experiences of recruitment and their decision to participate. Ideally, a researcher independent of the trial team would conduct and analyse an embedded qualitative study. However, given the trial was being undertaken as part of my PhD studies and the lack of alternative resources available, this was the only viable approach. Therefore, I considered any obvious and conscious bias I might present before conducting the research.

I appreciated that I was in a potential role of power due to my clinical relationship with patients, which may affect their responses during interview. Thus, I tried to maintain neutrality in the context of data collection, interpretation and presentation (269). I assured

[19] Constructivism is the perception that participants construct their knowledge from experiences and are in a constant state of revision (266).

all interviewees that I was conducting the interviews in my capacity as a researcher, rather than a dietitian, with a view to improving patient experience in future trials. I tried to maintain neutrality in wording during the interview and was conscious of my choice of words, for example referring to 'the study (team)' rather than the use of 'I' in relation to the design of the trial. The interviews were conducted at the patient's home or a place of their choosing, rather than the hospital, to minimise environmental bias. I also dressed to suit this environment, wearing casual clothing rather than my clinical uniform, to help emphasise the difference between my roles.

During this time, I maintained a reflective diary. I noted points of interest from the interviews, emotions displayed by patients and relatives and body language. I reflected upon my strengths and weaknesses as a researcher. These reflections aided the iteration of the topic guide and the development of my interview technique. The qualitative interviews led me to become more emotionally attached to patients. Rather than simply maintaining a clinical relationship, I visited their homes and met their family, which provided context to their lives that I would otherwise not have known.

When patients and relatives spoke negatively of the trial, I was able to remain impartial. From a personal view point, whilst I was the trial dietitian and KEATING was being undertaken as part of my PhD thesis, recruitment and retention were poor. Hence, I was keen to speak with patients who consented, patients who declined and their relatives to understand the challenges they faced and how they made their decision with a view to improving the support they received and inevitably improve KD trials going forward. The patients were an inspiration to me, their family and their peers.

To offer credibility and reliability to the results, the interpretation of themes was developed and tested through periodic discussion with two experienced qualitative researchers independent of the trial, as I led the process of iterating between the developing analysis and the new data.

I was very appreciative of interviewees' time and views. Without their participation in the interviews, this research would not be possible and no improvements would be made to the design of KD trials for patients with GBM.

5.4 RESULTS

5.4.1 Sample characteristics / contextual factors

Fifteen patients and their relatives were invited to be interviewed. Of these, 10 patients (66%) and five of their relatives, all of whom were white British, took part in interviews between January and April 2018. Of the patients, five were male and five female; of the relatives three were male and two female (see table 5.3). All participants were interviewed separately except one patient and one relative who were interviewed jointly. Individual interviews lasted for an average (median) of 44 minutes (36 - 62 minutes) and the dyad interview lasted 65 minutes. Average (median) time from initial contact about KEATING to the qualitative interview was 11.4 weeks (6.9 – 22 weeks), with those participants retrospectively recruited (T27 to T51) experiencing the longer delays (see table 5.3).

Those who were retained within KEATING were the youngest patients, those who declined were the older patients and those who withdrew were aged between those who retained and those who declined. The IMD (272) was also reviewed for each patient (eleven resided in England and four in Wales), as illustrated in table 5.3. Those who retained in the study and those who declined were generally from areas ranked of higher IMD, therefore less deprived areas of England and Wales, whilst those who withdrew were generally from areas ranked of lower IMD, thus more deprived areas of England and Wales.

Table 5.3: Patient and relatives' characteristics										
KEATING participant number	**Gender**	**Age (years)**	**IMD**	**KEATING intervention arm**	**KEATING categorisation**	**Time to interview (weeks)**	**Relative interviewed**	**Relative participant number**	**Gender**	**Relationship to participant**
T27	Female	60-69	1*	MKD	Early withdrawal	22	No	-	-	-
T30	Female	70-79	>50%ǂ	-	Declined	22	Yes	T30/R	Male	Husband
T35	Female	50-59	4*	-	Declined	17.1	No	-	-	-
T39	Female	60-69	30-50%ǂ	MKD	Delayed withdrawal	10.2	Yes	T39/R	Male	Husband
T44	Male	40-49	2*	MKD	Continued participation	14.4	No	-	-	-
T45	Male	40-49	7*	MCT KD	Continued participation	12.6	Yes	T45/R	Female	Wife
T47	Female	60-69	2*	MKD	Delayed withdrawal	9.7	Yes	T47/R	Male	Husband
T51	Male	50-59	10*	MCT KD	Continued participation	6.9	Yes	T51/R	Female	Wife
T52	Male	60-69	2*	MCT KD	Early withdrawal	8.1	No	-	-	-
T55	Male	60-69	8*	-	Declined	9.3	No	-	-	-

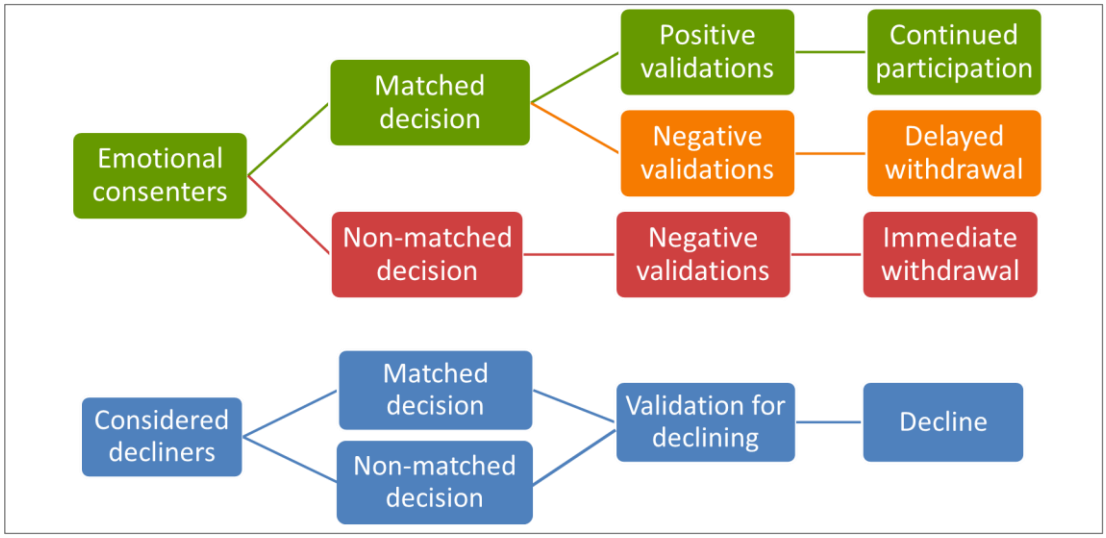
Abbreviations: IMD = Index of Multiple Deprivation; MCT KD= medium chain triglyceride ketogenic diet; MKD= modified ketogenic diet.

Key: Continued participation = continued with the intervention beyond three months; Early withdrawal = withdrew from the trial following consent and randomisation, but prior to commencing a KD; Delayed withdrawal = withdrew from the trial after commencing KD but before the primary end point of three months; Declined = declined to participate in KEATING. Time to interview = time from initial contact about KEATING to qualitative interview. *Index of Multiple Deprivation (England): decile of 1 = 10% most deprived areas of England, decile of 10 = 10% least deprived areas of England; ǂ Index of Multiple Deprivation (Wales): 10% = 10% most deprived areas of Wales, >50% = >50% least deprived areas of Wales.

5.4.2 Patients' accounts of their decision-making regarding participating in KEATING

Linked to the study aims, patients' accounts of their decision-making are presented according to the outcome of their decision about KEATING: i) continued participation; ii) early withdrawal; iii) delayed withdrawal; and iv) declined participation. The relationships between these decisions are illustrated in figure 5.1. Throughout the results, verbatim quotes are presented in speech marks, with ellipses indicating missing text and square brackets indicating replacement or explanatory text. To preserve anonymity, all patients were identified by the patient's KEATING trial number (e.g. T01) and relatives by an associated number (e.g. T01/R).

Figure 5:1 Qualitative pictorial of decision-making patterns



Key: Emotional consenters = patients who consented to participate in KEATING, intuitively; Considered decliners = patients who declined to participate in KEATING who were considered and deliberative in their decision-making. Matched decision = the decision of the patient is supported by their relative; Non-matched decision = decision of the patient is opposing to that of the relative; Positive validations = positive experiences or encounters which positively influence the patients' decision to continue participating in the trial; Negative validations = negative experiences or encounters which negatively influence the patients' decision to continue participating in the trial; Continued participation = continued with the intervention beyond three months; Early withdrawal = withdrew from the trial following consent and randomisation, but prior to commencing a KD; Delayed withdrawal = withdrew from the trial after commencing KD but before the primary end point of three months; Declined = declined to participate in KEATING.

5.4.3 Continued participation

The initial decision of the three patients who continued to participate in KEATING (beyond the twelve week primary end point) was recalled as being instantaneous: *"I jumped in, you know, took the opportunity with both hands … it was a no brainer"* (T44). One explained their reaction to hearing about the trial as *"give me a straw and I'll grasp anything"* (T51). They emphasised that participating in the trial provided the opportunity for them to *"fight for their life"* (T44), otherwise "*if I don't do this I'm sure as eggs is eggs I'm not going to be here"* (T51). The patients wanted to commence the diet immediately and reported the feasibility nature of the trial to be largely irrelevant: *"… [the research team are] doing your study for the feasibility of people doing it, rather than what I'm doing it for, which is to turnaround and maximise the health benefits"* (T45). Their decision about trial participation was reportedly different to how they would normally make a decision; as illustrated by T51, patients did not appear to consider the risks of participating, only the benefits: "*there were no risks…I know the National Health Service are ultra-cautious, they have to be don't they… benefits well there's a small chance I might live*" (T51). These patients explained how taking part in the trial and following a KD offered them control over their condition: *"I have no real options when it comes to the medical side of it you know, you've got to take their best advice. The idea of doing the diet, so that you had some control, was appealing you know" (T44).*

After making their initial decisions, the three patients in this group reported seeking approval from their family: *"it was a case of speaking to my family and getting their support to make sure that they were on board with what I was going to do, my family gave me the thumbs [up]"* (T44). Relatives of those patients who continued to participate in the trial supported the patients' decision: *"[we would do] anything that works, to be honest, we'd give anything a go"* (T45/R).

Randomisation to MKD or MCT KD was recalled to be clearly understood by most patients who continued to participate and reportedly held no bearing over their decision to participate, with one patient commenting *"we have no real idea which is the best"* (T51). Those randomised to MCT KD and thus consuming nutritional products as part of the diet, explained that these products helped them because *"I don't know if I'd have had the confidence or the ability to do the diet perhaps without the supplement to start with, because doing your weights and measures for the entire diet I think must be quite difficult"* (T45).

Patients in this group also spoke to making an ongoing decision to participate on a regular basis. They also spoke of the importance of positive opinions of 'informed' relatives and

online blogs in this process. As T51 recalled, *"we've got a friend who's an oncologist nurse…and she put us in touch with a blogger, erm, so a guy that survived this, he's 12 months down the track"*. All three patients also made reference to the influence of 'positive stories' from long term KD GBM patient survivors: *"there's lot of good results of people having positive responses to it [ketogenic diet]… the one story was the guy who had a, erm had the same tumour, he's on this [ketogenic diet], his [tumour] reduced, what's not to want to go for that?"* (T45). They also recalled seeking approval from clinicians, because: *"if we get this wrong, that costs me my life, you don't make decisions on things that you're not fully up to speed with. [Consultant's name] was the guy in my eyes [to talk to about the trial]"* (T44). These three patients who chose to remain in the trial also recounted having self-researched KEATING, the diet, other clinical trials and holistic treatments after consenting to participate.

As time passed, the reasons attributed to participation initially became the reasons patients recalled for continued participation, along with new factors such as *"obviously benefits are research for the greater good"* (T45) and *"losing weight and staying fit and active is definitely the way forward"* (T44). Patients reported feeling *"more mentally astute and more confident at dealing with this [diagnosis] going forward"* (T51) and spoke of being motivated to continue because *"my first scan was so positive"* (T51). Patients explained their motivation for following the diet each day through *"long term goals"* (T44), with ketones providing *"a quick confidence check and every now and again"* (T45) and offering 'fulfilment', alongside experiencing a "*fantastic quality of life with cancer"* (T44). These three patients reported these factors to be more important than what food they ate: "*I don't care if I have to eat cheese nuts and celery every lunch time, it doesn't bother me"* (T44). Patients reported enjoying the 'dietary regime', explaining that "*I don't need a sneaky chocolate bar and that's for the variety, so I'm actually enjoying the comfort of regimental approach"* (T44). As a family, relatives emphasised the diet to be "*a new normal for us"* (T45/R). The patients attributed their ability to 'cope' to the support provided by their relatives, as T45 explained: *"I get to a point where I'm being a bit tired, so [relatives' name] will regularly come in and say do you want ketone bun and having [wife] there she will go along [and cook]".* These patients who retained in the trial expressed remaining satisfied with their initial decision.

5.4.4 Early withdrawal

Two patients consented to KEATING but withdrew early after being randomised and receiving dietary education, but before commencing the diet. Consistent with those who continued to participate in KEATING, the two who withdrew early described their initial decision to

participate as being *"more of a gut decision"* (T52) or based on *"gut instinct"* (T27), because *"[I] don't want to die so I'll try anything at the moment"* (T52). As T27 explained, *"initially, [I] was like anything to help and I thought the diet could help, you know because I was full of 'oh let's do this' and… it was a gut instinct I think… because if it was going to do me good and I was hoping I could do it, maybe sort of slow it [cancer] down"* (T27).

These two patients also described feeling satisfied and *"felt very confident"* (T27) with their initial decision. It was at a later stage, following dietary education and after discussing their decision with a relative, that they decided to withdraw, explaining that, on reflection, they had begun *"stressing myself out"* (T27) over the decision to continue participating in the trial and had started to feel as though "*it was just too much, I was just trying to take too much on"* (T52).

Both patients explained they felt that they would be reliant on the relative to assist them with the diet and monitoring during a 'busy' time, and this added to their 'worry' about participating in the trial, as T27 explained: *"I wasn't doing cooking… so it was all [husband], erm and putting that pressure on him as well, when he was already worrying about me and trying to look after me. I didn't want to put that pressure on him."* (T27). Similarly, T52 reflected that *"just preparing [meals] and trying to sort out where I was at [was a concern] because [relative's name] got her own family and things going on so it was just down to me"* (T52). They also spoke of their tendency to 'comfort eat', explaining *"I'd would just curl up on the couch Sunday and think well I'll just have a cup of tea and a biscuit… open a packet of biscuits and they would be gone within twenty minutes"* (T52). Both spoke about feeling concerned about how to adhere to the diet, because *"it's a fact that you've got to scratch your head and work out what you want to eat and what you're going to fancy eating because some of it doesn't taste that nice…"* (T52). They described 'struggling' with *"thinking about well, what can I eat instead"* (T27), which added to their worry because "*[I] was thinking too much about it and worrying what I was going to replace the carbs with"* (T27).

Upon making the decision to withdraw, both patients described again feeling confident and relived: *"it was like, erm, a big relief that I'd made that decision"* (T27). Both patients also went on to explain that their relatives did not wish them to participate in the trial and agreed with their decisions to withdraw: *"[husband's] opinion was just concentrate on getting yourself better, you don't need that as well to think about, that might be too much… so yes he wasn't very happy about me wanting to do it"* (T27). However, they reflected that their relatives had no influence on their ultimate decision to withdraw from the trial: *"he didn't*

have an influence because I'm very strong" (T27). Interestingly, following early withdrawal, both patients also recalled making dietary changes which they felt to be in line with the principles of KEATING, but which seemed reasonable and attainable to their lifestyle: *"a sweet tooth is my main problem but now I've cut them [biscuits] all out"* (T52) and *"it's all the carbs, I eat a lot of bread, I'm trying to cut down at the moment"* (T27).

5.4.5 Delayed withdrawal

Two patients withdrew after consenting to KEATING and following the diet for approximately six weeks. They also recalled their initial decision about trial participation to be instantaneous and different to how they usually make decisions: "*I thought about it but not as long as I would normally, I sort of made a decision on that day that I was going to have a go at it"* (T47). In keeping with those who retained and those who withdrew before starting the diet, participants described choosing to participate in the trial because it *"would be beneficial for me"* (T47). They were able to state the aim of the trial and recalled "*no promises were made at all… just research and they explained about the pilot scheme"* (T39). However, both recounted believing that *"there's a chance that changing the way we are eating would have an impact [on cancer]"* (T39), and described considering the benefits of the trial, but not the risks: *"well, I understood the benefits of it because of the cancerous cells… and the risks? I'm not really sure about the risks."* (T47).

These two patients also explained that they had adequate time afterwards to consider their decision but this did not alter their initial decision. They spoke of discussing their decision to participate with their relative. All felt that they had been influenced by their relatives' opinion, stating *"I wouldn't have done it [participated] on my own"* (T39) and that *"we had a discussion together as to whether or not we felt it was the right thing for me to do… [relative] just supported me with it, he felt that I should be giving it a go as well"* (T47). Like the patients, relatives also described their decisions as instantaneous: "*I'd take anything with open arms because anything that would help cure [the tumour], you know… I'd jump at."* (T47/R), with relatives attributing a kind of selfishness to their motives: "*I wanted her to have a go… I suppose it's a bit selfish really but you know you, there's a selfish element in it because you want her to be here sort of thing"* (T39/R). The two relatives recalled their understanding of the trial's aim to be "*to assist the chemotherapy and radiation treatment she was getting… and assist the chemotherapy to cure, well, to cure it… that's why we sort of we're keen to get on the diet"* (T47/R) and to "*help as regards, erm, wellbeing, you know, for the person"* (T39/R). The relatives explained that they were prepared to support the patient with the

requirements of the trial - *"all the preparation and err the shopping and cooking that was all down to me"* (T47/R) - and to provide moral support: *"I had to be there to encourage, to back up when things were a bit flat"* (T39/R). Patients reported appreciating that they would require support from their relative to undertake the trial, as T47 explained: "*I think it did help having a support behind me because obviously I had to rely on him for getting all the correct foods in and cooking it for me"* (T47).

The patients' understanding of randomisation was mixed. One reported an understanding of the process, rationale and intervention arms, explaining that *"no personal bias or anything at all was coming into it, [it] was just totally, totally at random like scientific…done [on] computer"* (T39). The other solely recalled an understanding of the two arms, recalling that *"I know one of them was I might have to drink, the other food"* (T47). Both patients and relatives in this group reported a preference towards one intervention or the other and MCT nutritional products (Betaquik, Vitaflo [International] Ltd) were viewed both positively (showing favour towards MCT KD) and negatively (showing favour towards MKD), as illustrated in the following quotes:

> *"[I] just didn't fancy the drinks with the fat… just the thought of drinking fats, you know, through liquid and the one that I was on was just solid food and food that I liked… I don't think I'd've lasted as long as I did"* (T47).

> *"Well it was have either the full fat drink or go on the food. [Patient] preference all along I think was the food… so that could put people off when they think that… [Patient] was dreading the thought of going on a fat one, I think"* (T47/R).

Both patients recounted how they or their relatives undertook their own research using online search engines after consenting to participate: "*I did go on Google and did a little bit of research"* (T47); *"then of course our daughter [researched the study] on Google… next thing we had a cookery book arrived and I think another one arrived, erm so she was sort of…trying to help"* (T39). These patients also spoke of the influence of online blogs on their decision to participate, explaining: *"well there's this guy… I knew that he'd been doing the ketone diet as well and he felt like it worked for him. So I read his blog it encouraged me that it actually worked for him, so it encouraged me to take part in it [the study]"* (T47).

The patients spoke about the importance of their clinical teams supporting the study: *"it was nice to know that you had the backing of the doctors and nurses as well… in the medical profession… good to know they back you"* (T39), and the perceived 'safety' of a trial as it was

being undertaken by healthcare professionals *"I was going to try something but like when he explained about this [the trial] I though that's even better because you've got professionals behind you… I thought well you know somebody who knows what they're talking about so I felt safer if you like"* (T39).

As time progressed within the trial, initial dietary preferences could change with experience: *"we perhaps [would have] gone maybe a bit for the supplement side [MCT KD] had we known that's it more difficult to actually do the diet"* (T39/R). Indeed, these patients described feeling 'worried' about what they could eat and the effect of this on their mental wellbeing: *"I was worrying, I was waking up, I was literally waking up… and that's all I could think about: 'Oh I've got to get my fats intake today'. And that's all I was thinking about and erm it was pulling me down"* (T39). Relatives reported sharing this worry and concern for the patients' wellbeing: *"in the end the diet made her feel a bit down…that didn't help the condition… it wasn't a burden but… it was very stressful for [patient] and, you know, it knocks on to yourself doesn't it, because you want to help or you want to help them as much as you can… if it impacts in that sort of [way] it's a problem then"* (T39/R). Patients and relatives recalled taking day-to-day motivation from ketone measurements, but perceiving a lack of results. They reported feeling 'demoralised' when the readings were low. The relative of T47 recalls their experience:

> *"You don't see any results, the only results that we were seeing was, as little as they was, was [patient's name] waterworks. Whether or not we were achieving that level [of ketones] that you wanted to be at and that was that was the only motivation that we could see that was actually working and the blood count whether or not that was working. So they're the motivation. If you achieve that then you think you've done something that week… the low ketones it made me feel personally that I wasn't doing the diet right… it demoralised you"* (T47/R).

Both patients reflected that they felt as though they needed to try the diet to understand the 'reality' of participating in the trial: *"you had to try the diet to discover how difficult [it was], I didn't realise it would be that difficult"* (T39). Both patients and relatives reported that following either KD would be difficult to *"live with that forever more"* (T47). Relatives reported sharing similar thoughts: *"so you don't know when you're going into it whether or not you're going to be able to do it, until you try it. And fair play she tried it and she couldn't continue"* (T47/R). Both patients emphasised that they found the diet 'harsh' and 'monotonous' and described lacking enjoyment from eating: *"I think it was the restriction*

and harshness of the food really…it's just totally alien to the way I eat" (T39). They also reported encountering difficulties during festive periods which affected their compliance: *"Christmas came up I think and with everything there's treatment going on and the diet and Christmas and it's a busy time anyway so I think it maybe that was just unfortunate"* (T39). Both patients and relatives reflected that the duration of the diet was too long to sustain their continuation on the trial: "*I'd say the only criticism I've got is that it's possibly too long on the diet*" (T47/R).

Both patients recalled discussing their withdrawal from the trial with their relative. After withdrawing from the trial, patients described feeling "*free again like I could make my own decisions on what I was going to eat... it was a burden having to have just the same type of food all the time"* (T39), and "*so much better and I think [relative's name] did too because he was a bit concerned about me"* (T47). Despite this, neither patient in this group reported regretting their initial decision and would undertake the trial again. Like those who withdrew prior to starting the diet, these patients also reported changing what they ate following withdrawal from KEATING in ways that inclined towards a KD, such as reducing high carbohydrate foods, but were more attainable than a full KD.

5.4.6 Declined participation

In comparison to those who consented, the three patients who declined KEATING described being considered and deliberate in their decisions, consistently describing a lack of perceived personal benefit from participation: *"the only thing I think about this study is erm what would benefit me"* (T35); *"if you were to say to me I guarantee that, I guarantee that, I guarantee you're going to be, better, you know, I might even do it"* (T55). They read the information sheet and were able to understand the aims of the trial to be exploring feasibility. They stated being 'unconvinced' by the research and that they were unlikely to experience any improvements in their quality of life. Patient T30 summarised this in their quote:

> *"I thought well you've got to try these things but on the other hand I'm not convinced, yeah I'm not really convinced about it at all erm and I've not heard anybody convinced which is unfair isn't it? I haven't heard anybody say, "listen this works and it certainly works for these people" or whatever, whatever, and I'm thinking, well and also I suppose because I'm sceptical about these things a bit… yeah I suppose there isn't enough evidence really who it works with. Well, it probably won't improve my quality of life. It's not answering questions because it's too low key to answer the right questions… if you can come back in a couple of years down and say it is beneficial, you know, after your studies...."* (T30).

They described feeling that they would be poor trial candidates due to their dietary preferences: *"when I read through the thing [patient information sheet]… I just realised I'm going to be dreadful. I mean, I've never dieted in my life… me go down to 5 or 10% carbohydrates diet? Not going to happen. Not eating crisps, chips, potatoes? Not going to happen"* (T55). Lifestyle and socialising were also factors reportedly considered by those who declined: *"there's my social life which involves, you know, going round to somebody's house for dinner so you know they are going to put food in front of me and if I start saying "oh I don't like this and I don't like that" they're going to wonder who they've invited round"* (T55).

All three patients commented upon reasons why other patients might participate, such as being younger in age and having dependent children: *"Certainly if I was 30 or 40 I might have a completely different attitude to it. You know, if I had a young family and everything you might be saying, well, you know, "anything, I will do anything at all to try and defeat this thing" but, you know, I'm just at a different stage in life really now"* (T55). They speculated personality to play a role on participation: *"I mean all the patients I've seen going for cancer treatment are very buoyant so they're I think they're up for anything that helps them"* (T30/R). They also commented on how other patients may perceive the trial and 'play the game' in a different way to them: *"you can see why people would go down the road of they'd trying anything to see does it work… to each his own. Everybody plays a game differently"* (T30).

Those who declined also explained that quality of life was more important to them than quantity and referred to the impact of their age on their decision: *"you get to around 70 years old and that's where I am. So now every day I get up I want a quality day…you know, so quality of life is something I'm into right now…and so having a complex regime around diet again it doesn't appeal"* (T55). One viewed the trial as *"a waste of your life"* (T35), but reflected that they may consider participating for *"half of the time"* (T35). They considered that "*younger people will be much more keyed into this study than we are"* (T30).

Two recalled the time commitment and the impact to their family caused by dietary changes to be 'off putting': *"I did want to do it but I was, kind of, 'will I have time for this?' and I'm tired… I thought 'can I fit all this in?' and that was holding me back a little bit… my husband's doing everything in here. I thought 'oh I don't want to start changing. I've got to eat this and I've got to eat that.'"* (T35). All three group of patients also discussed how the media influenced their perception of KDs and therefore their decision to take part in KEATING: *"I did see the television programme a while ago… the guy on the low carbohydrate diet was*

serious cause for concern after six months….and people like Sky Cycling Team said they'd never put anyone on a diet like that its unsafe" (T55).

All patients discussed how they avoided finding out about their condition and prognosis to reduce worry: *"All the way through this [disease] I've not gone online I don't want to know about it [glioblastoma] …every now and then I see correspondence between consultants and GP and stuff and all so I think they're just naturally gloomy a lot of medics so I don't want to worry"* (T55). They explained how they wanted to continue with their life: *"I don't want information, I don't want anything, I just want to go on with my life, that's how we addressed it"* (T30).

The three who declined also recalled having discussed the trial with their relative, with two of the relatives agreeing with their decision in relation to quality of life, as illustrated in the following quotes: *"I did discuss it with my wife… and I think at the end of the day, you know, she said her main thing was quality of life yeah"* (T55); *"well I think it's something to be worthwhile but, erm, I was a bit concerned that it was a very restrictive diet for my wife to take at this stage really"* (T35/R). These patients all reported feeling satisfied with their decision to decline. For the remaining patient, their decision to decline was not in agreement with their relative's opinion and this patient described weighing up the 'pros and cons' of the trial continuously and feeling uncertain over their decision. T35 described this in their account:

> *"My sister and my husband and my daughter… would encourage me [to take part in KEATING]. She [relative] was saying, you know, "you should read it all and you should go through it and it's supposed to be a really good study" and I said "I will, I will one day when I get some energy back"… because I wanted to do it but I didn't know if I could do it…I kept thinking 'oh because I've got that many appointments, have I got time to go to the Walton Centre to talk about what I should be doing as a diet?' But then I think 'well if I've got benefits from it yes you should', you know what I mean?"* (T35).

As with those who withdrew from the study, all patients who declined also considered making dietary changes after declining to participate in KEATING: *"I just really want to be going forward and eating properly and you know not having too many carbs and stuff like"* (T35). Some reported making different dietary choices: *"I have rebalanced a bit instead of meat and that, so many days, I've got fish twice a week now… some recipes for vegetarian options"* (T35/R). Some suggested ideas for 'reasonable' dietary changes in trials going forward: *"if it was structured differently if you were to say to me look my advice would be cut*

down on your carbohydrate and eat these foods and rebalance your diet a bit more… I could certainly do that to a certain extent, you know, like I wouldn't eat two bags of crisps, I would only have one" (T55).

5.5 DISCUSSION

This qualitative study explored patients' accounts of their decision-making, comparing those who chose to participate in KEATING and those who declined. It also explored the influences of relatives on these decisions and changes in patients' decision-making over time.

All patients who consented to participate in KEATING described making their initial decision to participate instantaneously and without deliberation. This reflects what others have reported about the decision-making of advanced cancer patients in early phase trials (241,244) and the decision-making of other cancer populations (273). These reported accounts of the patients who consented to KEATING stand in contrast to the patient decision-making processes outlined by Gillies et al. (236). Instead, the decisions of patients who consented to KEATING were shaped by fear of GBM and of not having done all they could to 'fight' for their lives. These fears activated an emotional decision-making heuristic: participating in the trial initially provided hope for a cure and optimism for prolonging life and reducing fear of death and regret (274). Altruism was not considered, which is reflective of other advanced cancer populations (241,242,244,245). Those who consented initially exaggerated the possible health and personal benefits, which optimistically biased their interpretation of the aims and objectives of the trial (245) and could result in questionable informed consent. However, the influence of hope and optimism on the decisions of advanced cancer patients has also been noted in other studies and may not necessarily invalidate their informed consent (244,245,275), with one study which explored end-of-life conversations with long term GBM survivors finding a wish to 'live as long as possible' and prolong life to be important, as in KEATING (276). Adopting an optimistic stance reflects more general life optimism, and can be adaptive for patients as it may help them to cope with their prognosis (251,253,277,278). Challenging this optimism and coping strategy may be demoralising for some patients. Clinicians should continue to use their clinical judgement when considering if patients' consent to participate in a trial is informed or not. There is currently little guidance offered by the Health Research Authority (HRA) Good Clinical Practice guidelines (279) regarding this matter.

In contrast, those patients who declined to participate in KEATING did not make an emotional decision. Instead they described being considered and deliberate in their decision-making

process. They weighed up the perceived risks and benefits and perceived quality of life, rather than quantity of life, to be of the upmost importance, which is in keeping with other brain cancer research (242,280) and with theory described by Gillies et al. (236). Interestingly, although those who declined were older in age compared to those who consented and altruism did not appear to influence their decision-making. This conflicts with previous studies which report altruism as a key reason for older adults participating in dietary clinical trials, however the findings of Fearn et al. (2010) were based on general older adults rather than older adults living with cancer (281).

Following their initial decision, all patients sought to validate their decision by seeking the opinion of others. Patients particularly sought approval from their spouse or partner, regardless of whether the patient consented or declined to participate in the trial. If the relative's decision matched the patient's decision, then patients reported feeling satisfied and confident with their decisions. This conflicts with pre-consent 'deliberation' discussed in previous studies, with deliberation occurring after the patients' initial decision, and highlights the role of relatives in patients' decision-making processes (211,236,282). Interestingly, what patients sought from their relative varied, with some reporting seeking approval only, whilst others described wanting to share decision-making and relying on their relative to assist them with their decision. In some cases, the relative offered support for the patient, and in one case, conflicting opinions led patients to deliberate and reconsider their initial decision (283). Previous studies have found those patients who prefer to make a shared decision with a relative regarding healthcare to be from areas of lower IMD, which is also reflective of the KEATING population (247). However, there is currently a lack of data exploring the influence of relatives on the decision of patients with advanced cancer to participate in early phase clinical trials. Godskesen et al., (2013) are the only group to discuss the influence and even then relatives themselves were not interviewed (244).

Patients also sought validation for their decision to participate from an 'informed relative' with pre-existing healthcare or research knowledge, a phenomena previously noted in other studies (245). Given the influence of relatives on patients' decision-making, further multi-perspective qualitative research would be beneficial to explore this concept further (284,285). In addition to seeking the views of their relatives, those who consented began to reflect upon their decision in an altruistic manner, considering their family and young children (254,285). This consideration to dependants appeared to be influenced by a desire to have 'tried everything' (241,245,276), and is in keeping with 'death anxiety' noted in

previous glioma studies (286) and the perceived positive activism of long term cancer survivors (287).

Most consenting patients also sought the opinion and approval of a clinician. They trusted the clinician's opinion and viewed the clinician as a supportive member of their decision-making process, illustrating the role of relational autonomy in validation of their choice (235,288). This element of clinician trust can also be noted in other early phase clinical trials (242,244,245).

After commencing the diet, patients continued to review and validate their own decision, whether this was to continue to participate in KEATING or to withdraw. Those who continued to participate in KEATING beyond three months (primary end-point) reported finding validation from the media, blogs of long-term KD GBM survivors, clinical imaging and high ketone levels. To the authors' knowledge, this type of ongoing validation has not been previously described in the context of trial participation. In contrast to those who found ketone monitoring to be motivating and a source of validation, those who withdrew from KEATING reported uncertainty and a lack of validation from ketone monitoring, reporting low ketones to be 'demoralising', with the decision to withdraw motivated by a need to avoid prolonged impacts on their quality of life. Although a desire to extend quantity of life influenced the initial decisions for these patients to participate, quality of life became more important as the trial progressed, in keeping with other brain cancer research (242,280). Those who withdrew reported finding the diet difficult to cope with compared to the adaptive lifestyle of those who continued to participate. Those who withdrew also reported emotional eating habits compared to the functional eating habits of those who continued in the trial. Those who withdrew from the trial and those who declined were clear that the trial period of three months was too long. Patients reported 'feeling free again' once the diet was discontinued. It is important to note, that this may not necessarily equate to dietary acceptability outside of a clinical trial. In a future post-trial environment, information regarding the efficacy of the diet may be available, which could alter patients' willingness to engage.

Despite withdrawing from the trial or declining to participate, all patients reported making dietary changes. There was no evidence base to support this health initiative, which is a point of interest, given that a lack of evidence for KDs was one of the reasons for declining participation.

5.5.1 Strengths and limitations

This study has several strengths. It is the first study to explore patients' experiences of KDs, and their decisions to enter and continue in KD trials for GBM. It is also one of few qualitative studies involving an early phase trial to compare the accounts of patients who consented with those who declined. Patients highlighted the role of relatives in patient decision-making and in supporting them with the trial. Through interviewing patients and relatives as a dyad we were able to explore this relationship from both viewpoints.

There are also several limitations to this study. Firstly, the sample size was small and we cannot be certain that saturation was achieved. Nevertheless, drawing on the concept of 'information power' (258,259) in qualitative research, this study had a well specified aim, and it has provided insights which will be valuable in informing a future phase III trial.

Further, with regards to sampling, five patients declined to participate in the qualitative study (two due to declined health, two declined research participation and one due to the burden of a visit), four of which had declined to participate in KEATING. Given the decline in health of two of the patients, our sample may be considered to only represent the views of 'healthier' patients with GBM.

As the qualitative study was embedded eight months after KEATING opened to recruitment, the views of initial KEATING patients remain unknown. It is possible that the verbal recruitment strategy changed over time as the researcher became more familiar with the process; therefore the views of those recruited into KEATING first may be different to those recruited towards the end of the recruitment period. Due to this delay in embedding the qualitative study logistically its main aim was to inform strategies to optimise and support the decision-making of patients invited to participate in future KD trials for patients with GBM, rather than inform the KEATING trial itself.

As some patients were interviewed up to three months after their decision about KEATING, they may have found it hard to accurately recall their decision-making process, particularly given the nature of their condition and the numerous other decisions they will likely have had to make regarding their care and treatment. Finally, both the qualitative study and KEATING were conducted by the same researcher, which may have influenced patients' willingness to be critical of KEATING or otherwise affected the trustworthiness of the qualitative study (270,271). However, all patients expressed criticisms of KEATING. In

addition, researchers who were independent of KEATING (GC and BY) were closely involved in the qualitative study and in scrutinising the interpretations of the data.

Interviewees were not asked to read through their own accounts after transcription to seek the transcript being a true representation of their accounts. This was secondary to the nature of their illness and speed of progression, which would be an ethical concern.

5.6.1 Implications

The findings of this study have several implications for subsequent KD trial design and conduct for patients with GBM. In order to optimise patients' decision-making and informed consent to trials, researchers planning and working on future trials should consider the following suggestions:

5.6.1.1 Suggestions to optimise the decision-making processes of patients

- Efforts to optimise informed consent could be aided through the design of bespoke decision aids (236,289). Given our findings that some patients were dependent upon their relative to aid their decision, and all patients are reliant upon their relative to help implement the diet to an extent, including the relative in initial and ongoing conversations about trial participation (with the agreement of the patient), could also help to optimise patient decision-making.
- The views of clinicians who will be actively recruiting patients should also be explored as stakeholders to future recruiting trials, as their views currently remain unknown.

5.6.1.2 Suggestions to optimise study design

- Some patients reported decreased motivation after six weeks, whilst those who declined requested a shorter trial period. Evidence in animal models demonstrates KD to be most effective concomitant to radiotherapy (79). As such, a six week, rather than twelve week, trial period should be considered by future KD trials for patients with GBM.
- Some patients expressed a personal preference for or against the use of MCT nutritional products. Therefore, it may be beneficial to allow the patients to choose whether they choose to use such products to support a KD and this option requires further exploration in a GBM population.
- Future trials should embed a longitudinal prospective qualitative study into the trial design phase, which focuses on patient and relative understanding and decision-making in the context of trial participation. This would help to identify and address challenges as they arise in future trials.

5.6.1.3 Clinical implications

- Exploring the views of clinicians in the wider organisation and multi-disciplinary team where future interventions may be delivered will likely be essential for the implementation of KD services in neuro-oncology and for ensuring clinician 'buy in'.

5.7 CONCLUSION

This embedded qualitative study explored the decision-making of patients invited to participate in KEATING and their relatives. Future KD trials for patients with GBM can draw on these findings to ensure the decision-making of patients is optimised and adequately supported. The role of relatives in this decision and in supporting patients with the implementation of the trial should not be underestimated. A shorter intervention period of six weeks may be more attainable.

CHAPTER 6

SUMMARY, RECOMMENDATIONS AND CONCLUSIONS

6.1 CHAPTER OVERVIEW

The use of ketogenic diets (KDs) for patients with glioblastoma (GBM) was an important question and in keeping with the James Lind Alliance Neuro-Oncology Priority Setting Partnership research priorities (1). This thesis set out to explore i) the evidence for efficacy and acceptability of KDs for patients with gliomas; ii) the level of patient interest to support a randomised controlled trial (RCT); iii) the deliverability of a KD intervention in an NHS setting; iv) the feasibility of a trial protocol (KEATING) and the impact this trial would have on patients with GBM; and v) patients' perspectives of their decision-making when invited to participate in KEATING.

In this chapter, the headline results and conclusions will be discussed and recommendations to optimise the design of future trials will be proposed, prior to offering concluding remarks.

6.2 SUMMARY

The overall aim of this thesis was to explore the feasibility of using KDs as an adjuvant therapy for patients with GBM. Whilst the preliminary survey and scoping service highlighted the level of patient interest to be adequate to support a RCT and that KDs could be delivered to patients with glioma within an NHS setting, the practicality of running a KD trial for patients with GBM proved challenging.

KEATING initially faced challenges with recruitment, falling below the progression criteria for a phase III RCT. Whilst eventually meeting the recruitment target one month ahead of schedule, the rate of recruitment to KEATING (28.6%) was below that of large NIHR-HTA funded oncology trials (50 to 89%) (290). Dietary retention rates were also poor, with 33% of patients completing the three month trial period. This further affected the completeness of trial data and subsequent analysis.

A qualitative study was embedded to explore the challenges facing recruitment in further detail and proved pivotal in understanding the decision-making of patients invited to participate in KEATING. The initial progression criteria for KEATING were based entirely on quantitative outcomes; yet it is also important to consider how the findings from the qualitative study may impact upon the decision of feasibility and the design of future trials.

Screening data at the start of KEATING revealed patients were declining due to i) not wanting to participate in research; ii) the burden of dietitian visits; and iii) the burden of KD. Whilst these where similar to the barriers noted in the patient survey (chapter 3), an in depth understanding was considered vital to improve trial design and the patient experience. During the qualitative study those patients who declined appeared considered and deliberate in their decision-making process, taking time to consider their options. They spoke of the importance of quality of life; a reason which was not reported in the basic screening log explanations in the quantitative results from KEATING. Quality of life was also not included as a possible barrier during the patient survey. This highlights the effects of researcher bias in survey design (156) and the value of qualitative research in addition to trials, surveys and PPI (291).

The qualitative study also offered insights into why patients decided to take part in KEATING, with these patients describing their initial decision as being instantaneous and without deliberation. Patients spoke of wanting to 'fight' for their lives and their decisions were shaped by a fear of GBM. Participating offered hope and optimism for prolonging life. Patients initially exaggerated the health benefits of participating, which optimistically biased their interpretation of the aims and objectives of the trial. Altruism was considered by those who participated, but as a means of validation, later in their decision-making process; contradicting the initial survey, in which altruism was the top reason for participating in a KD trial. This willingness to help others features strongly as a reason for being interested in trials, but altruism is often conditional to person benefit when actually attending recruitment appointments and taking part in a trial (292).

Alongside issues with recruitment, dietary retention within KEATING was also poor (33% at three months; n=4), particularly in comparison to the initial scoping service (67% at three months; n=4) (169). The average time to withdrawal during KEATING was 38 days (medium chain triglyceride ketogenic diet [MCT KD]) and 39.5 days (modified ketogenic diet [MKD]). The GBM population recruited for the scoping service, self-selected to try the diet, with half having completed chemoradiotherapy for GBM. Hence, the scoping service population may have been more motivated or engaged with KD, than the general GBM population approached for KEATING, resulting in false optimism for trial success. Reasons for withdrawal during KEATING were noted to be due to dietary burden (n=3), nausea (n=1), tumour progression (n=1), being recruited to another trial (n=1), non-related serious adverse event (SAE; n=1) and a patient reported to have changed their mind, no further information was provided (n=1). The qualitative study offered further insight into these higher than anticipated withdrawal rates. Those who withdrew spoke of finding low ketones 'demoralising', withdrawing due to the negative effect this feeling had on their quality of life. Previous studies report quality of life to become increasingly important to patients over the brain cancer journey (242,280). During KEATING, quality of life was not reported as a factor for withdrawal, perhaps due to the insensitivity of the predefined case report from, although from the QLQ-C30 questionnaire, the global health status of those who withdrew reduced, falling below the brain cancer reference value at week six. These results substantiate the findings from the qualitative study, but due to the small sample size limited conclusions can be drawn. For those who continued to participate in the trial, global health status reduced within the MCT KD group and improved for the patient following MKD. Both groups reported experiencing a 'fantastic quality of life' when interviewed for the qualitative study, describing

the diet to offer a sense of 'control'. They found motivation for continuing with the diet through media outputs, online blogs of long term survivors, clinical imaging and high ketone levels and used this as a means of validating their decision. This corroborates the findings from KEATING, in that patients with higher ketones stayed in the trial, whilst those with lower ketones withdrew early, at around week six. Those who were retained in KEATING were also generally younger in age and had good prognostic characteristics, which may also have influenced their ability to retain within the study and implement the diet.

Those who withdrew also considered the three-month intervention to be undesirable, an opinion also reflected by those who declined, further corroborating the findings from KEATING. A shorter, six week intervention, is likely to be more attainable and agreeable to the majority of patients. This could be offered alongside radiotherapy and concomitant chemotherapy, which coincides with the proposed optimal time for the diet derived from animal model data (79).

The qualitative study also revealed the role of relatives in the patients' decision-making process when invited to participate in KEATING, with patients seeking validation from relatives regarding decisions to participate, decline, and withdraw. In some cases, patients shared the decision to participate with their relative, appreciating that they would require assistance to implement the diet. This is an interesting area of research which requires further investigation as there is currently a lack of data exploring the role of relatives in the decision-making of patients with advanced cancers to participate in early phase pilot trials (244). Relatives were also key in supporting patients to implement the diet. For those patients who continued to participate in KEATING, relatives emphasised KD to be 'the new normal'. Patients attributed their ability to cope with KD being due to the support provided by relatives, but those who withdrew, later reported feeling that they had overburdened their relative, which influenced their decision to withdraw. The role of relatives, both in the decision-making of patients and the ongoing support offered, were aspects that were underappreciated in the KEATING study.

The preliminary findings from KEATING highlight that there may be a potential role for MCT supplements in aiding dietary retention, since more patients in the MCT KD arm completed the three month intervention, however patient numbers were limited (n=3 MCT KD; n=1 MKD). Volumes of MCT equating to 25% of total energy requirements appear tolerable. However, during the qualitative study, patients and their relatives spoke of having a

personal preference towards MCT supplements and a preconception of how well the supplements may be tolerated. As a result, future trials may benefit from tailoring supplement use to the individuals' preferences, rather than randomising to MKD or MCT KD, but further exploration in this area would be beneficial to understand if patient choice over supplement use would increase or alleviate their burden.

This thesis has several limitations. In relation to the survey, non-random, convenience sampling was used at Walton Centre NHS Foundation Trust and patients self-selected to complete the online national survey, both of which could create a positive bias in the results. In relation to the scoping service, the small numbers of patients included were self-selecting, self-referring patients, who commenced MKD at different time-points in their treatment pathway, limiting the generalisability of our results in the context of the glioblastoma population as a whole. This also led to an optimistic bias for the trial team, when determining recruitment targets and the sample size for KEATING.

For KEATING, due to the high withdrawal rates at around week six, a post-hoc analysis was introduced to extrapolate further information, to help explore issues with dietary retention and improve future trial design. Due to the poor retention rates only limited analysis could be undertaken at months three and 12. The lack of returned food and ketone diaries also became problematic and subsequently affected the 12 month analysis. All accounts of dietary intake were also self-reported, and so at risk of reporter bias (227). The food acceptability questionnaire, whilst validated for use in vegan diets, was not validated for use in KDs.

Finally, the qualitative study used a small sample size determined by the number of patients approached for KEATING and the nature of their deteriorating health. We cannot be certain that saturation was reached. Nevertheless, drawing on the concept of 'information power' (258,259) in qualitative research, this study had a well specified aim, and it has provided insights that will be invaluable in informing future phase III trials. As the qualitative study was embedded eight months after KEATING opened to recruitment, the views of initial KEATING patients remain unknown. It is possible that the verbal recruitment strategy changed over time as the researcher became more familiar with the process; therefore the views of those recruited into KEATING at the start, may be different to those recruited towards the end of the recruitment period. Both the qualitative study and KEATING were conducted by the same researcher, which may have influenced patients'

willingness to be critical of KEATING or otherwise affected the trustworthiness of the qualitative study (270,271). However, all patients expressed criticisms of KEATING. In addition, researchers who were independent of KEATING were closely involved in the qualitative study and in scrutinising the interpretations of the data.

6.3 RECOMMENDATIONS

To expand and develop the themes explored in this thesis, future studies should consider the following recommendations:

- To assess efficacy in a phase III trial a six–week diet intervention period would be advantageous. Some patients reported decreased motivation after six weeks, whilst those who declined requested a shorter trial period. As animal models show KD to enhance the positive effects of radiotherapy, it would be reasonable to offer KD during this time within the confines of a trial. Future trials assessing efficacy should also consider a health economic assessment, with NICE requiring new technologies to be both clinically and cost effective.
- The trial took time to embed within the clinical practice, therefore recruitment figures were initially slow. Future trials could consider a staged, incremental recruitment rate to compensate for this issue. An 'upstream' approach to trial design may improve recruitment practices and clinical team engagement.
- Efforts to optimise informed consent could be aided through the design of bespoke decision aids, a means of helping patients to make informed decisions about participating in a ketogenic clinical trial, taking into account personal preferences and values (236,289). Including the relatives in the initial and ongoing conversations about trial participation (with the agreement of the patient), could also help to optimise patient decision-making.
- Future trials should embed a longitudinal, prospective, qualitative study, which focuses on patient and relative understanding and decision-making in the context of trial participation. This would help to identify and address challenges as they arise in future trials.
- Exploring the views of clinicians in the wider organisation and multi-disciplinary team, where future ketogenic trials may be delivered, will likely be essential for the implementation of KD services in neuro-oncology and for ensuring clinician 'buy in'.
- There may be a role for MCT supplements in improving dietary retention, but volume of supplements should be considered. Paediatric levels cannot be tolerated by

adults, but volumes equating to 25% of total energy requirements appear acceptable. Some patients expressed a personal preference for or against the use of MCT nutritional products. It may be beneficial to allow the patients to choose whether to use such products to support a KD and this option requires further exploration in a GBM population.

- There is interest from the glioma patient community to support clinical trials with KD interventions; however randomisation to a control arm of 'no diet' could affect recruitment. Further patient and public involvement (PPI) would be critical to ensure trial methods are acceptable to patients. Further PPI would also be beneficial to explore if digital media would aid the completion of food and ketone diaries. PPI should involve patients who have tried KDs before and their relatives/ carers, but also patients for whom KD would be new, a view point which is essential if dietary retention and trial completion rates are to be improved. Combining PPI with qualitative research may help to engage patients who would not usually participate in research (291).

6.4 CONCLUSION

Recruitment of patients with GBM to a KD trial is possible. To assess efficacy in a clinical trial, a six week intervention period is proposed. Future KD trials for patients with GBM can draw on the findings of this thesis to ensure the decision-making of patients is optimised and adequately supported. The role of relatives in the patients' decision-making process and in supporting patients to implement KDs should not be underestimated. Further qualitative studies embedded within phase III clinical trials are essential to optimise trial design and patient experience. Future phase III trials would benefit from an internal pilot to further test the recommendations derived from KEATING.

REFERENCES

1. Macdonald L. Top 10 priorities for clinical research in primary brain and spinal cord tumours: Final report of the James Lind Alliance Priority Setting Partnership in Neuro-Oncology [Internet]. 2015 [cited 2018 Dec 11]. Available from: www.neuro-oncology.org

2. Ostrom QT, Bauchet L, Davis FG, Deltour I, Fisher JL, Langer CE, et al. The epidemiology of glioma in adults: a “state of the science” review. Neuro Oncol. 2014;16(May):896–913.

3. Brodbelt A, Greenberg D, Winters T, Williams M, Vernon S, Collins VP, et al. Glioblastoma in England : 2007 – 2011. Eur J Cancer [Internet]. 2015;51(4):533–42. Available from: http://dx.doi.org/10.1016/j.ejca.2014.12.014

4. Davis ME. Glioblastoma: Overview of Disease and Treatment. Clin J Oncol Nurs [Internet]. 2016 [cited 2019 Jul 16];20(5 Suppl):S2-8. Available from: http://www.ncbi.nlm.nih.gov/pubmed/27668386

5. Schiff D, Lee EQ, Nayak L, Norden AD, Reardon DA, Wen PY. Medical management of brain tumors and the sequelae of treatment. Neuro Oncol [Internet]. 2015 Apr [cited 2019 Jul 16];17(4):488–504. Available from: http://www.ncbi.nlm.nih.gov/pubmed/25358508

6. Louis DN, Perry A, Reifenberger G, von Deimling A, Figarella-Branger D, Cavenee WK, et al. The 2016 World Health Organization Classification of Tumors of the Central Nervous System: a summary. Acta Neuropathol. 2016;131(6):803–20.

7. National Institute for Health and Care Excellence. Brain tumours (primary) and brain metastases in adults (NG 99) [Internet]. NICE; 2018 [cited 2019 Jan 7]. Available from: https://www.nice.org.uk/guidance/ng99

8. Hegi ME, Diserens A-C, Gorlia T, Hamou M-F, de Tribolet N, Weller M, et al. *MGMT* Gene Silencing and Benefit from Temozolomide in Glioblastoma. N Engl J Med [Internet]. 2005 Mar 10 [cited 2019 Jan 7];352(10):997–1003. Available from: http://www.ncbi.nlm.nih.gov/pubmed/15758010

9. Monga V, Jones K, Ph D, Chang S. Clinical relevance of molecular markers in gliomas. Rev Clínica Las Condes [Internet]. 2017;28(3):343–51. Available from: http://dx.doi.org/10.1016/j.rmclc.2017.05.003

10. Young RM, Jamshidi A, Davis G, Sherman JH. Current trends in the surgical management and treatment of adult glioblastoma. Ann Transl Med [Internet]. 2015 Jun [cited 2019 Jul 16];3(9):121. Available from: http://www.ncbi.nlm.nih.gov/pubmed/26207249

11. Schiff D, Lee EQ, Nayak L, Norden AD, Reardon DA, Wen PY. Medical management of brain tumors and the sequelae of treatment. Neuro Oncol. 2015 Apr;17(4):488–504.

12. Davis ME. Glioblastoma: Overview of Disease and Treatment. Clin J Oncol Nurs. 2016;20(5 Suppl):S2-8.

13. Kreth FW, Thon N, Simon M, Westphal M, Schackert G, Nikkhah G, et al. Gross total but not incomplete resection of glioblastoma prolongs survival in the era of radiochemotherapy†. Ann Oncol [Internet]. 2013 Dec 1 [cited 2019 Jan 23];24(12):3117–23. Available from: http://www.ncbi.nlm.nih.gov/pubmed/24130262

14. Vuorinen V, Hinkka S, Färkkilä M, Jääskeläinen J. Debulking or biopsy of malignant glioma in elderly people - a randomised study. Acta Neurochir (Wien) [Internet]. 2003 Jan 1 [cited 2019 Jan 23];145(1):5–10. Available from: http://link.springer.com/10.1007/s00701-002-1030-6

15. Sanai N, Chang S, Berger MS, Parsa AT, Berger MS. An extent of resection threshold for newly diagnosed glioblastomas. J Neurosurg [Internet]. 2011 Aug [cited 2019 Feb 1];115(1):1–18. Available from: http://www.ncbi.nlm.nih.gov/pubmed/21417701

16. Weller M, van den Bent M, Hopkins K, Tonn JC, Stupp R, Falini A, et al. EANO guideline for the diagnosis and treatment of anaplastic gliomas and glioblastoma. Lancet Oncol [Internet]. 2014 Aug 1 [cited 2019 Jan 23];15(9):e395-403. Available from: http://www.ncbi.nlm.nih.gov/pubmed/25079102

17. Kubben PL, ter Meulen KJ, Schijns OE, ter Laak-Poort MP, van Overbeeke JJ, Santbrink H van. Intraoperative MRI-guided resection of glioblastoma multiforme: a systematic review. Lancet Oncol [Internet]. 2011 Oct 1 [cited 2019 Jan 23];12(11):1062–70. Available from: https://www.sciencedirect.com/science/article/pii/S1470204511701309

18. Senft C, Bink A, Franz K, Vatter H, Gasser T, Seifert V. Intraoperative MRI guidance and extent of resection in glioma surgery: a randomised, controlled trial. Lancet Oncol [Internet]. 2011 Oct [cited 2019 Feb 1];12(11):997–1003. Available from: http://www.ncbi.nlm.nih.gov/pubmed/21868284

19. Laperriere N, Zuraw L, Cairncross G, Cancer Care Ontario Practice Guidelines Initiative Neuro-Oncology Disease Site Group. Radiotherapy for newly diagnosed malignant glioma in adults: a systematic review. Radiother Oncol [Internet]. 2002 Sep [cited 2019 Jan 23];64(3):259–73. Available from: http://www.ncbi.nlm.nih.gov/pubmed/12242114

20. Roa W, Brasher PM., Bauman G, Anthes M, Bruera E, Chan A, et al. Abbreviated Course of Radiation Therapy in Older Patients With Glioblastoma Multiforme: A Prospective Randomized Clinical Trial. J Clin Oncol [Internet]. 2004 May 1 [cited 2019 Jan 23];22(9):1583–8. Available from: http://www.ncbi.nlm.nih.gov/pubmed/15051755

21. Stupp R, Mason WP, van den Bent MJ, Weller M, Fisher B, Taphoorn MJB, et al. Radiotherapy plus Concomitant and Adjuvant Temozolomide for Glioblastoma. N Engl J Med [Internet]. 2005;352(10):987–96. Available from: http://www.nejm.org/doi/abs/10.1056/NEJMoa043330

22. Stupp R, Brada M, van den Bent M, Tonn J, Pentheroudakis G. High-grade glioma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol [Internet]. 2014 [cited 2017 Jan 9];0(0):1–9. Available from: http://annonc.oxfordjournals.org/content/early/2014/04/29/annonc.mdu050.full.pdf

23. Hart MG, Garside R, Rogers G, Stein K, Grant R. Temozolomide for high grade glioma. Cochrane Database Syst Rev [Internet]. 2013 Apr 30 [cited 2019 Jan 23];(4). Available from: http://doi.wiley.com/10.1002/14651858.CD007415.pub2

24. Malmström A, Grønberg BH, Marosi C, Stupp R, Frappaz D, Schultz H, et al. Temozolomide versus standard 6-week radiotherapy versus hypofractionated radiotherapy in patients older than 60 years with glioblastoma: the Nordic randomised, phase 3 trial. Lancet Oncol [Internet]. 2012 Sep 1 [cited 2019 Jan

23];13(9):916–26. Available from: https://www.sciencedirect.com/science/article/pii/S1470204512702656

25. Wick W, Platten M, Meisner C, Felsberg J, Tabatabai G, Simon M, et al. Temozolomide chemotherapy alone versus radiotherapy alone for malignant astrocytoma in the elderly: the NOA-08 randomised, phase 3 trial. Lancet Oncol [Internet]. 2012 Jul [cited 2019 Feb 1];13(7):707–15. Available from: http://www.ncbi.nlm.nih.gov/pubmed/22578793

26. Wen PY, Chang SM, Van den Bent MJ, Vogelbaum MA, Macdonald DR, Lee EQ. Response Assessment in Neuro-Oncology Clinical Trials. J Clin Oncol [Internet]. 2017 Jul 20 [cited 2019 Jan 23];35(21):2439–49. Available from: http://www.ncbi.nlm.nih.gov/pubmed/28640707

27. Gilbert MR, Dignam JJ, Armstrong TSTS, Wefel JS, Blumenthal DT, Vogelbaum MA, et al. A randomized trial of bevacizumab for newly diagnosed glioblastoma. N Engl J Med. 2014;370(8):699–708.

28. Taal W, Oosterkamp HM, Walenkamp AME, Dubbink HJ, Beerepoot L V, Hanse MCJ, et al. Single-agent bevacizumab or lomustine versus a combination of bevacizumab plus lomustine in patients with recurrent glioblastoma (BELOB trial): a randomised controlled phase 2 trial. Lancet Oncol [Internet]. 2014 Aug 1 [cited 2019 Jan 23];15(9):943–53. Available from: https://www.sciencedirect.com/science/article/pii/S1470204514703146

29. Krex D, Klink B, Hartmann C, Von Deimling A, Pietsch T, Simon M, et al. Long-term survival with glioblastoma multiforme. Brain. 2007;130(10):2596–606.

30. Bush NAO, Chang SM, Berger MS. Current and future strategies for treatment of glioma. Neurosurg Rev [Internet]. 2017 Jan 16 [cited 2019 Jan 31];40(1):1–14. Available from: http://link.springer.com/10.1007/s10143-016-0709-8

31. Westphal M, Hilt DC, Bortey E, Delavault P, Olivares R, Warnke PC, et al. A phase 3 trial of local chemotherapy with biodegradable carmustine (BCNU) wafers (Gliadel wafers) in patients with primary malignant glioma. Neuro Oncol [Internet]. 2003 Apr 1 [cited 2019 Jan 31];5(2):79–88. Available from: http://academic.oup.com/neuro-oncology/article/5/2/79/1070081/A-phase-3-trial-of-local-chemotherapy-with

32. Bruce JN, Fine RL, Canoll P, Yun J, Kennedy BC, Rosenfeld SS, et al. Regression of Recurrent Malignant Gliomas With Convection-Enhanced Delivery of Topotecan. Neurosurgery [Internet]. 2011 Dec 1 [cited 2019 Jan 31];69(6):1272–80. Available from: https://academic.oup.com/neurosurgery/article-lookup/doi/10.1227/NEU.0b013e3182233e24

33. Vogelbaum MA, Aghi MK. Convection-enhanced delivery for the treatment of glioblastoma. Neuro Oncol [Internet]. 2015 Mar 1 [cited 2019 Jan 31];17(suppl 2):ii3-ii8. Available from: https://academic.oup.com/neuro-oncology/article-lookup/doi/10.1093/neuonc/nou354

34. Stupp R, Hegi ME, Gorlia T, Erridge SC, Perry J, Hong YK, et al. Cilengitide combined with standard treatment for patients with newly diagnosed glioblastoma with methylated MGMT promoter (CENTRIC EORTC 26071-22072 study): a multicentre, randomised, open-label, phase 3 trial. Lancet Oncol. 2014;15(10):1100–8.

35. Hanahan D, Weinberg RA. Hallmarks of Cancer: The Next Generation. Cell [Internet]. 2011 Mar 4 [cited 2019 Jan 31];144(5):646–74. Available from:

https://www.sciencedirect.com/science/article/pii/S0092867411001279

36. Weller M, Butowski N, Tran DD, Recht LD, Lim M, Hirte H, et al. Rindopepimut with temozolomide for patients with newly diagnosed, EGFRvIII-expressing glioblastoma (ACT IV): a randomised, double-blind, international phase 3 trial. Lancet Oncol [Internet]. 2017 Oct 1 [cited 2019 Feb 1];18(10):1373–85. Available from: http://www.ncbi.nlm.nih.gov/pubmed/28844499

37. Phuphanich S, Wheeler CJ, Rudnick JD, Mazer M, Wang H, Nuño MA, et al. Phase I trial of a multi-epitope-pulsed dendritic cell vaccine for patients with newly diagnosed glioblastoma. Cancer Immunol Immunother [Internet]. 2013 Jan 31 [cited 2019 Jan 31];62(1):125–35. Available from: http://link.springer.com/10.1007/s00262-012-1319-0

38. Omuro A, Vlahovic G, Lim M, Sahebjam S, Baehring J, Cloughesy T, et al. Nivolumab with or without ipilimumab in patients with recurrent glioblastoma: results from exploratory phase I cohorts of CheckMate 143. Neuro Oncol [Internet]. 2018 Apr 9 [cited 2019 Feb 1];20(5):674–86. Available from: http://www.ncbi.nlm.nih.gov/pubmed/29106665

39. Ung N, Yang I. Nanotechnology to augment immunotherapy for the treatment of glioblastoma multiforme. J Neurooncol [Internet]. 2015 Jul 13 [cited 2019 Jan 31];123(3):473–81. Available from: http://link.springer.com/10.1007/s11060-015-1814-1

40. Stupp R, Taillibert S, Kanner AA, Kesari S, Steinberg DM, Toms SA, et al. Maintenance Therapy With Tumor-Treating Fields Plus Temozolomide vs Temozolomide Alone for Glioblastoma A Randomized Clinical Trial. JAMA J Am Med Assoc. 2015;314(23):2535–43.

41. Taphoorn MJB, Dirven L, Kanner AA, Lavy-Shahaf G, Weinberg U, Taillibert S, et al. Influence of Treatment With Tumor-Treating Fields on Health-Related Quality of Life of Patients With Newly Diagnosed Glioblastoma. JAMA Oncol [Internet]. 2018 Apr 1 [cited 2019 Jan 29];4(4):495. Available from: http://oncology.jamanetwork.com/article.aspx?doi=10.1001/jamaoncol.2017.5082

42. Bernard-Arnoux F, Lamure M, Ducray F, Aulagner G, Honnorat J, Armoiry X. The cost-effectiveness of tumor-treating fields therapy in patients with newly diagnosed glioblastoma. Neuro Oncol [Internet]. 2016 [cited 2019 Feb 1];18(8):1129–36. Available from: http://www.ncbi.nlm.nih.gov/pubmed/27177573

43. Mehta M, Wen P, Nishikawa R, Reardon D, Peters K. Critical Reviews in Oncology / Hematology Critical review of the addition of tumor treating fields (TTFields) to the existing standard of care for newly diagnosed glioblastoma patients. Crit Rev Oncol / Hematol [Internet]. 2017;111:60–5. Available from: http://dx.doi.org/10.1016/j.critrevonc.2017.01.005

44. Aune D, Chan DSM, Lau R, Vieira R, Greenwood DC, Kampman E, et al. Dietary fibre, whole grains, and risk of colorectal cancer: systematic review and dose-response meta-analysis of prospective studies. BMJ [Internet]. 2011 Nov 10 [cited 2019 Jan 29];343:d6617. Available from: http://www.ncbi.nlm.nih.gov/pubmed/22074852

45. Kuan AS, Green J, Kitahara CM, Berrington de González A, Key T, Reeves G, et al. Diet and risk of glioma: combined analysis of three large prospective studies in the UK and USA. Neuro Oncol [Internet]. 2019 Jan 23 [cited 2019 Jan 29]; Available from: https://academic.oup.com/neuro-oncology/advance-

article/doi/10.1093/neuonc/noz013/5299220

46. The Brain Tumour Charity. Diet [Internet]. 2016 [cited 2019 Jan 29]. Available from: https://assets.thebraintumourcharity.org/live/media/filer_public/82/a4/82a45237-06ff-4c28-90a4-af3c91b5577c/diet-for-people-with-brain-tumours_-v3-factsheet.pdf

47. National Health Service. The Eatwell Guide [Internet]. 2019. [cited 2019 Jan 29]. Available from: https://www.nhs.uk/live-well/eat-well/the-eatwell-guide/

48. British Association for Parenteral and Enteral Nutrition (BAPEN). Malnutrition Universal Screening Tool [Internet]. 2006 [cited 2019 Jan 29]. Available from: www.bapen.org.uk

49. Qureshi M, Zelinski E, Carlson LE. Cancer and Complementary Therapies: Current Trends in Survivors' Interest and Use. Integr Cancer Ther [Internet]. 2018 Sep 9 [cited 2019 Jan 29];17(3):844–53. Available from: http://journals.sagepub.com/doi/10.1177/1534735418762496

50. The Bible. Roman Catholic Bible: New Testament. In: Roman Catholic Bible: New Testament [Internet]. 2018 [cited 2018 Dec 4]. Available from: https://www.biblegateway.com/passage/?search=Matthew+17%3A14-21%2CMark+9%3A14-29%2CLuke+9%3A37-43%2CLuke+17%3A6&version=EXB#en-EXB-23619

51. Guelpa G, Marie A. La lutte contre l'épilepsie par la désintoxication et par la rééducation alimentaire. Rev Ther Medico-Chirurgicale. 1911;78:8–13.

52. Geyelin HR. The treatment of epilepsy. JAMA J Am Med Assoc [Internet]. 1927 May 21 [cited 2018 Dec 4];88(21):1638. Available from: http://jama.jamanetwork.com/article.aspx?doi=10.1001/jama.1927.02680470024012

53. Martin-McGill K, Jackson C, Bresnahan R, Levy R, Cooper P. Cochrane Database of Systematic Reviews Ketogenic diets for drug-resistant epilepsy (Review). Cochrane Database Syst Rev [Internet]. 2018 [cited 2018 Nov 7];(11). Available from: www.cochranelibrary.com

54. National Institute for Health and Care Excellence (NICE). Epilepsies: diagnosis and management [Internet]. NICE; 2012 [cited 2018 Dec 7]. Available from: https://www.nice.org.uk/guidance/cg137

55. Martin-McGill KJ, Lambert B, Whiteley VJ, Wood S, Neal EG, Simpson ZR, et al. Understanding the core principles of a "modified ketogenic diet": a UK and Ireland perspective. J Hum Nutr Diet [Internet]. 2019 Mar 11 [cited 2019 Mar 18]; Available from: http://doi.wiley.com/10.1111/jhn.12637

56. Neal E. Dietary treatment of epilepsy. Practical implementation of ketogenic therapy. First edit. Chichester, UK: Wiley-Blackwell; 2012.

57. Kossoff EH, Zupec-Kania BA, Auvin S, Ballaban-Gil KR, Christina Bergqvist AG, Blackford R, et al. Optimal clinical management of children receiving dietary therapies for epilepsy: Updated recommendations of the International Ketogenic Diet Study Group. Epilepsia Open [Internet]. 2018 Jun [cited 2018 Oct 19];3(2):175–92. Available from: http://www.ncbi.nlm.nih.gov/pubmed/29881797

58. Kossoff EH, Dorward JL, Turner Z, Pyzik PL. Prospective Study of the Modified Atkins

Diet in Combination With a Ketogenic Liquid Supplement During the Initial Month. J Child Neurol [Internet]. 2011 Feb 10 [cited 2018 Oct 29];26(2):147–51. Available from: http://www.ncbi.nlm.nih.gov/pubmed/20833798

59. McDonald TJW, Henry-Barron BJ, Felton EA, Gutierrez EG, Barnett J, Fisher R, et al. Improving compliance in adults with epilepsy on a modified Atkins diet: A randomized trial. Seizure [Internet]. 2018 Aug 1 [cited 2018 Oct 30];60:132–8. Available from: https://www.sciencedirect.com/science/article/pii/S1059131118302346?via%3Dihub

60. Otto C, Kaemmerer U, Illert B, Muehling B, Pfetzer N, Wittig R, et al. Growth of human gastric cancer cells in nude mice is delayed by a ketogenic diet supplemented with omega-3 fatty acids and medium-chain triglycerides. BMC Cancer [Internet]. 2008;8:122. Available from: http://www.ncbi.nlm.nih.gov/pubmed/18447912%5Cnhttp://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=PMC2408928

61. Hao G-W, Chen Y-S, He D-M, Wang H-Y, Wu G-H, Zhang B. Growth of human colon cancer cells in nude mice is delayed by ketogenic diet with or without omega-3 fatty acids and medium-chain triglycerides. Asian Pacific J Cancer Prev. 2015;16(5).

62. Tisdale MJ, Brennan RA. A comparison of long-chain triglycerides and medium-chain triglycerides on weight loss and tumour size in a cachexia model. Br J Cancer [Internet]. 1988;58(5):580–3. Available from: http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=2246820&tool=pmcentrez&rendertype=abstract

63. Paganoni S, Wills A-M. High-fat and ketogenic diets in amyotrophic lateral sclerosis. J Child Neurol [Internet]. 2013 Aug [cited 2019 Jan 29];28(8):989–92. Available from: http://www.ncbi.nlm.nih.gov/pubmed/23666040

64. Appelberg KS, Hovda DA, Prins ML. The Effects of a Ketogenic Diet on Behavioral Outcome after Controlled Cortical Impact Injury in the Juvenile and Adult Rat. J Neurotrauma [Internet]. 2009 Apr 8 [cited 2019 Jan 29];26(4):497–506. Available from: http://www.liebertpub.com/doi/10.1089/neu.2008.0664

65. White H, Venkatesh B. Clinical review: Ketones and brain injury. Crit Care [Internet]. 2011;15(2):219. Available from: http://ccforum.biomedcentral.com/articles/10.1186/cc10020

66. Evangeliou A, Vlachonikolis I, Mihailidou H, Spilioti M, Skarpalezou A, Makaronas N, et al. Application of a Ketogenic Diet in Children With Autistic Behavior: Pilot Study. J Child Neurol [Internet]. 2003 Feb 2 [cited 2019 Jan 29];18(2):113–8. Available from: http://www.ncbi.nlm.nih.gov/pubmed/12693778

67. Taylor MK, Sullivan DK, Mahnken JD, Burns JM, Swerdlow RH. Feasibility and efficacy data from a ketogenic diet intervention in Alzheimer's disease. Alzheimer's Dement Transl Res Clin Interv [Internet]. 2018;4:28–36. Available from: https://doi.org/10.1016/j.trci.2017.11.002

68. Phillips MCL, Murtagh DKJ, Gilbertson LJ, Asztely FJS, Lynch CDP. Low-fat versus ketogenic diet in Parkinson's disease: A pilot randomized controlled trial. Mov Disord. 2018;33(8):1306–14.

69. Di Lorenzo C, Coppola G, Di Lenola D, Evangelista M, Sirianni G, Rossi P, et al. Efficacy

of Modified Atkins Ketogenic Diet in Chronic Cluster Headache: An Open-Label, Single-Arm, Clinical Trial. Front Neurol [Internet]. 2018 [cited 2019 Jan 29];9:64. Available from: http://www.ncbi.nlm.nih.gov/pubmed/29483892

70. Zahra A, Fath MA, Opat E, Mapuskar KA, Bhatia SK, Ma DC, et al. Consuming a Ketogenic Diet while Receiving Radiation and Chemotherapy for Locally Advanced Lung Cancer and Pancreatic Cancer: The University of Iowa Experience of Two Phase 1 Clinical Trials. Radiat Res [Internet]. 2017 Jun [cited 2019 Jan 29];187(6):743–54. Available from: http://www.ncbi.nlm.nih.gov/pubmed/28437190

71. Warburg O, Ding Y, Sharma J, Paetz MB, Meixensberger J, Gaunitz F, et al. THE METABOLISM OF TUMORS IN THE BODY. J Gen Physiol [Internet]. 1927 Mar 7 [cited 2017 Jan 25];8(6):519–30. Available from: http://www.jgp.org/cgi/doi/10.1085/jgp.8.6.519

72. Seyfried TN, Kiebish MA, Marsh J, Shelton LM, Huysentruyt LC, Mukherjee P. Metabolic management of brain cancer. Biochim Biophys Acta - Bioenerg [Internet]. 2011 Jun [cited 2016 Nov 15];1807(6):577–94. Available from: http://linkinghub.elsevier.com/retrieve/pii/S0005272810006857

73. Zhou W, Mukherjee P, Kiebish M, Markis W, Mantis J, Seyfried T. The calorically restricted ketogenic diet, an effective alternative therapy for malignant brain cancer. Nutr Metab [Internet]. 2007 [cited 2017 Jan 25];4(5). Available from: http://apps.webofknowledge.com.liverpool.idm.oclc.org/full_record.do?product=WOS&search_mode=GeneralSearch&qid=1&SID=X1qQmx8ojOU2JbzJk1q&excludeEventConfig=ExcludeIfFromFullRecPage&page=3&doc=74

74. Tisdale MJ, Brennan RA. Loss of acetoacetate coenzyme A transferase activity in tumours of peripheral tissues. Br J Cancer [Internet]. 1983 Feb [cited 2018 Dec 7];47(2):293–7. Available from: http://www.ncbi.nlm.nih.gov/pubmed/6130780

75. Allen BG, Bhatia SK, Anderson CM, Eichenberger-Gilmore JM, Sibenaller ZA, Mapuskar KA, et al. Ketogenic diets as an adjuvant cancer therapy: History and potential mechanism. Redox Biol. 2014;2(1).

76. Klement RJ, Champ CE, Otto C, Kämmerer U. Anti-tumor effects of ketogenic diets in mice: A meta-analysis. PLoS One. 2016;11(5):1–16.

77. Scheck AC, Abdelwahab MG, Fenton KE, Stafford P. The ketogenic diet for the treatment of glioma: Insights from genetic profiling. Epilepsy Res [Internet]. 2012 Jul [cited 2016 Nov 15];100(3):327–37. Available from: http://linkinghub.elsevier.com/retrieve/pii/S0920121111003044

78. Scheck AC, Abdelwahab MG, Stafford P, Kim D-Y, Iwai S, Preul M, et al. Mechanistic studies of the ketogenic diet as an adjuvant therapy for malignant gliomas. Cancer Res. 2011;70(Suppl 8):638.

79. Abdelwahab MG, Fenton KE, Preul MC, Rho JM, Lynch A, Stafford P, et al. The Ketogenic Diet Is an Effective Adjuvant to Radiation Therapy for the Treatment of Malignant Glioma. Canoll P, editor. PLoS One [Internet]. 2012 May 1 [cited 2016 Nov 15];7(5):e36197. Available from: http://dx.plos.org/10.1371/journal.pone.0036197

80. Woolf EC, Scheck AC. The ketogenic diet for the treatment of malignant glioma. J Lipid Res [Internet]. 2015 Jan [cited 2016 Nov 15];56(1):5–10. Available from: http://www.jlr.org/lookup/doi/10.1194/jlr.R046797

81. Vanitallie TB, Nufert TH. Ketones: Metabolism's Ugly Duckling. 2003 [cited 2017 Aug 8];327–41. Available from: http://coconutketones.com/wp-content/uploads/2016/10/7-Ketones-Metabolisms-ugly-ducking.pdf

82. St-Onge M-P, Jones PJH. Physiological effects of medium-chain triglycerides: potential agents in the prevention of obesity. J Nutr [Internet]. 2002 Mar 1 [cited 2017 Aug 8];132(3):329–32. Available from: http://www.ncbi.nlm.nih.gov/pubmed/11880549

83. Aminzadeh-Gohari S, Feichtinger RG, Vidali S, Locker F, Rutherford T, O'Donnel M, et al. A ketogenic diet supplemented with medium-chain triglycerides enhances the anti-tumor and anti-angiogenic efficacy of chemotherapy on neuroblastoma xenografts in a CD1-nu mouse model. Oncotarget [Internet]. 2017 Sep 11 [cited 2017 Sep 13];8(39):64728–44. Available from: http://www.oncotarget.com/fulltext/20041

84. Martuscello RT, Vedam-Mai V, Mccarthy DJ, Schmoll ME, Jundi MA, Louviere CD, et al. Cancer Therapy: Preclinical A Supplemented High-Fat Low-Carbohydrate Diet for the Treatment of Glioblastoma. Clin Cancer Res. 2015;22(10):2482–95.

85. Banjara M, Janigro D. Effects of the Ketogenic Diet on the Blood-Brain Barrier. In: Masino SA, editor. Ketogenic diet and metabolic therapies [Internet]. New York: Oxford University Press; 2017 [cited 2019 Jul 29]. p. 289–306. Available from: http://www.oxfordmedicine.com/view/10.1093/med/9780190497996.001.0001/med-9780190497996-chapter-30

86. Martin-McGill KJ, Srikandarajah N, Marson AG, Tudur Smith C, Jenkinson MD. The role of ketogenic diets in the therapeutic management of adult and paediatric gliomas: a systematic review. CNS Oncol [Internet]. 2018 Apr [cited 2018 Oct 15];7(2):CNS17. Available from: http://www.ncbi.nlm.nih.gov/pubmed/29658772

87. Nebeling LC, Miraldi F, Shurin S, Lerner E. Effects of a ketogenic diet on tumor metabolism and nutritional status in pediatric oncology patients: two case reports. J Am Coll Nutr [Internet]. 1995 Apr [cited 2016 Nov 15];14(2):202–8. Available from: http://www.ncbi.nlm.nih.gov/pubmed/7790697

88. Ville D, Chiron C, Laschet J, Dulac O. The ketogenic diet can be used successfully in combination with corticosteroids for epileptic encephalopathies. Epilepsy Behav [Internet]. 2015 Jul [cited 2019 Jul 16];48:61–5. Available from: http://www.ncbi.nlm.nih.gov/pubmed/26057351

89. McDonald TJ., Ratchford E V, Henry-Barron BJ, Kossoff EH, Cervenka MC. Impact of the modified Atkins diet on cardiovascular health in adults with epilepsy. Epilepsy Behav [Internet]. 2018;79:82–6. Available from: https://doi.org/10.1016/j.yebeh.2017.10.035

90. Alderman AK, Salem B. Survey Research. Plast Reconstr Surg [Internet]. 2010 Oct [cited 2018 Dec 18];126(4):1381–9. Available from: http://www.ncbi.nlm.nih.gov/pubmed/20885261

91. Jones TL, Baxter MAJ, Khanduja V. A quick guide to survey research. Ann R Coll Surg Engl [Internet]. 2013 Jan [cited 2018 Dec 18];95(1):5–7. Available from: http://www.ncbi.nlm.nih.gov/pubmed/23317709

92. O'Cathain A. A practical guide to using qualitative research with randomized controlled trials [Internet]. 1st ed. Oxford: Oxford University Press; 2018 [cited 2018

Sep 4]. Available from: https://global.oup.com/academic/product/a-practical-guide-to-using-qualitative-research-with-randomized-controlled-trials-9780198802082?cc=gb&lang=en&

93. Moore C, Carter, Neitert, Stewart. Recommendations for planning pilot studies in clinical and translational research. Clin Transl Sci. 2012;4(5):332–7.

94. Eldridge SM, Lancaster GA, Campbell MJ, Thabane L, Hopewell S, Coleman CL, et al. Defining Feasibility and Pilot Studies in Preparation for Randomised Controlled Trials : Development of a Conceptual Framework. PLoS One. 2016;11(13):1–22.

95. Wason JMS, Jaki T. Optimal design of multi-arm multi-stage trials. Stat Med. 2012;31:4269–79.

96. Magirr D, Stallard N, Jaki T. Flexible sequential designs for multi-arm clinical trials. Stat Med. 2014;33:3269–79.

97. O'Cathain A, Hoddinott P, Lewin S, Thomas KJ, Young B, Adamson J, et al. Maximising the impact of qualitative research in feasibility studies for randomised controlled trials: Guidance for researchers. Pilot Feasibility Stud. 2015;1(1):1–13.

98. Drabble SJ, O'Cathain A, Thomas KJ, Rudolph A, Hewison J. Describing qualitative research undertaken with randomised controlled trials in grant proposals: A documentary analysis. BMC Med Res Methodol. 2014;14(1).

99. Hubbard G, O'Carroll R, Munro J, Mutrie N, Haw S, Mason H, et al. The feasibility and acceptability of trial procedures for a pragmatic randomised controlled trial of a structured physical activity intervention for people diagnosed with colorectal cancer: Findings from a pilot trial of cardiac rehabilitation versus usua. Pilot Feasibility Stud [Internet]. 2016;2(1):1–15. Available from: http://dx.doi.org/10.1186/s40814-016-0090-y

100. Lewin S, Glenton C, Oxman AD. Use of qualitative methods alongside randomised controlled trials of complex healthcare interventions: Methodological study. BMJ. 2009;339(7723):732–4.

101. Hackshaw-Mcgeagh LE, Sutton E, Persad R, Aning J, Bahl A, Koupparis A, et al. Acceptability of dietary and physical activity lifestyle modification for men following radiotherapy or radical prostatectomy for localised prostate cancer: A qualitative investigation. BMC Urol. 2017;17(1):1–11.

102. Treweek S, Wilkie E, Craigie A, Caswell S, Thompson J, Steele R, et al. Meeting the challenges of recruitment to multicentre, community-based, lifestyle-change trials: a case study of the BEWEL trial. Trials. 2013;14(436):2–11.

103. Terranova CO, Lawler SP, Spathonis K, Eakin EG, Reeves MM. Breast cancer survivors' experience of making weight, dietary and physical activity changes during participation in a weight loss intervention. Support Care Cancer. 2017;25(5):1455–63.

104. Shingler E, Hackshaw-McGeagh L, Robles L, Persad R, Koupparis A, Rowe E, et al. The feasibility of the Prostate cancer: Evidence of Exercise and Nutrition Trial (PrEvENT) dietary and physical activity modifications: A qualitative study. Trials. 2017;18(1):1–10.

105. Mills N, Donovan JL, Smith M, Jacoby A, Neal DE, Hamdy FC. Perceptions of equipoise are crucial to trial participation: a qualitative study of men in the ProtecT

study. Control Clin Trials [Internet]. 2003 Jun 1 [cited 2018 Aug 20];24(3):272–82. Available from: https://www.sciencedirect.com/science/article/pii/S0197245603000205

106. Donovan J. Quality improvement report: Improving design and conduct of randomised trials by embedding them in qualitative research: ProtecT (prostate testing for cancer and treatment) study * Commentary: presenting unbiased information to patients can be difficult. BMJ [Internet]. 2002;325(7367):766–70. Available from: http://www.bmj.com/cgi/doi/10.1136/bmj.325.7367.766

107. Avery KNL, Donovan JL, Horwood J, Neal DE, Hamdy FC, Parker C, et al. The importance of dietary change for men diagnosed with and at risk of prostate cancer: a multi-centre interview study with men, their partners and health professionals. BMC Fam Pract [Internet]. 2014 May 3 [cited 2018 Aug 21];15:81. Available from: http://www.ncbi.nlm.nih.gov/pubmed/24886169

108. Boland A, Cherry MG, Dickson R. Doing a Systematic Review. First. London: SAGE Publications Ltd; 2014.

109. Armstrong R, Hall BJ, Doyle J, Waters E. "Scoping the scope" of a cochrane review. J Public Health (Bangkok). 2011;33(1):147–50.

110. Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. BMJ [Internet]. 2009 [cited 2017 Jan 12];339(b2535). Available from: http://www.bmj.com/content/339/bmj.b2535.full?view=long&pmid=19622551

111. Guo B, Moga C, Harstall C, Schopflocher D. A principal component analysis is conducted for a case series quality appraisal checklist. J Clin Epidemiol [Internet]. 2016 Jan [cited 2017 Jan 23];69:199–207.e2. Available from: http://www.ncbi.nlm.nih.gov/pubmed/26307459

112. Brooks KS, Woolf EC, Scheck AC. The Ketogenic Diet as an Adjuvant Therapy for Brain Tumors and Other Cancers. In: Critical Dietary Factors in Cancer Chemoprevention [Internet]. Cham: Springer International Publishing; 2016. p. 89–109. Available from: http://link.springer.com/10.1007/978-3-319-21461-0_5

113. Cohen JE, Wakefield CE, Cohn RJ. Nutritional interventions for survivors of childhood cancer. In: Cohen JE, editor. Cochrane Database of Systematic Reviews [Internet]. Chichester, UK: John Wiley & Sons, Ltd; 2016 [cited 2017 Jan 25]. Available from: http://doi.wiley.com/10.1002/14651858.CD009678.pub2

114. Dang MTMT, Wehrli S, Dang CVCV, Curran T, Taylor R, Bailey C, et al. The Ketogenic Diet Does Not Affect Growth of Hedgehog Pathway Medulloblastoma in Mice. Xie J, editor. 2015 Jul 20 [cited 2017 Jan 25];10(7):e0133633. Available from: http://dx.plos.org/10.1371/journal.pone.0133633

115. Fine EJ, Segal-Isaacson CJ, Feinman RD, Herszkopf S, Romano MC, Tomuta N, et al. Targeting insulin inhibition as a metabolic therapy in advanced cancer: A pilot safety and feasibility dietary trial in 10 patients. Nutrition [Internet]. 2012 Oct [cited 2017 Jan 25];28(10):1028–35. Available from: http://linkinghub.elsevier.com/retrieve/pii/S0899900712001864

116. Klement RJ, Fink MK. Dietary and pharmacological modification of the insulin/IGF-1 system: Exploiting the full repertoire against cancer. Oncogenesis. 2016;5.

117. Schmidt M, Pfetzer N, Schwab M, Strauss I, Kämmerer U. Effects of a ketogenic diet on the quality of life in 16 patients with advanced cancer: A pilot trial. Nutr Metab (Lond) [Internet]. 2011 Jul 27 [cited 2019 Mar 13];8(1):54. Available from: http://www.ncbi.nlm.nih.gov/pubmed/21794124

118. Seyfried BtN, Kiebish M, Marsh J, Mukherjee P. Targeting energy metabolism in brain cancer through calorie restriction and the ketogenic diet. J Cancer Res Ther [Internet]. 2009 [cited 2016 Nov 15];5(9):7. Available from: http://www.cancerjournal.net/text.asp?2009/5/9/7/55134

119. Nebeling LC, Lerner E. Implementing A Ketogenic Diet Based on Medium-chain Triglyceride Oil in Pediatric Patients with Cancer. J Am Diet Assoc [Internet]. 1995 Jun;95(6):693–7. Available from: http://linkinghub.elsevier.com/retrieve/pii/S0002822395001891

120. Artzi M, Liberman G, Vaisman N, Bokstein F, Vitinshtein F, Aizenstein O, et al. Changes in cerebral metabolism during ketogenic diet in patients with primary brain tumors: 1H-MRS study. J Neurooncol [Internet]. 2017 Jan 10 [cited 2017 Jan 26]; Available from: http://link.springer.com/10.1007/s11060-016-2364-x

121. Shen V, Tran L, Brown J. HG-32USE OF KETOGENIC DIET AS A COMPLIMENTARY METABOLIC THERAPY DURING CHEMO-RADIATION THERAPY IN A 7 YEAR OLD FEMALE WITH GLIOBLASTOMA. Neuro Oncol [Internet]. 2016 Jun 12 [cited 2017 Jan 26];18(suppl 3):iii54.3-iii54. Available from: http://neuro-oncology.oxfordjournals.org/lookup/doi/10.1093/neuonc/now073.29

122. Kalamian M, Zupec-Kania B, Favara BE, Liepa GU. Ketogenic diet as adjunctive therapy for brain tumors. First Int Symp Diet Treat Epilepsy other Neurol Disord Poster Present. 2008;1.

123. Attar H, Rolfe S, Marsey M, Rogers L. Results of the modified atkins diet in patients with recurrent glioma: Retrospective review. Neurology [Internet]. 2016 [cited 2017 Jan 26];86(16). Available from: https://hdas.nice.org.uk/strategy/124016/8/EMBASE/72250907

124. Champ CE, Palmer JD, Volek JS, Werner-Wasik M, Andrews DW, Evans JJ, et al. Targeting metabolism with a ketogenic diet during the treatment of glioblastoma multiforme. J Neurooncol [Internet]. 2014 Mar 19 [cited 2016 Nov 15];117(1):125–31. Available from: http://link.springer.com/10.1007/s11060-014-1362-0

125. Rieger J, Bähr O, Maurer GGD, Hattingen E, Franz K, Brucker D, et al. ERGO: A pilot study of ketogenic diet in recurrent glioblastoma. Int J Oncol [Internet]. 2014 Apr 11 [cited 2017 Jan 24];45(6):1843–52. Available from: http://www.spandidos-publications.com/10.3892/ijo.2014.2382

126. Schwartz K, Chang HT, Nikolai M, Pernicone J, Rhee S, Olson K, et al. Treatment of glioma patients with ketogenic diets: report of two cases treated with an IRB-approved energy-restricted ketogenic diet protocol and review of the literature. Cancer Metab [Internet]. 2015 Dec 25 [cited 2017 Jan 26];3(3):1–10. Available from: http://www.cancerandmetabolism.com/content/3/1/3

127. Strowd RE, Cervenka MC, Henry BJ, Kossoff EH, Hartman AL, Blakeley JO. Glycemic modulation in neuro-oncology: experience and future directions using a modified Atkins diet for high-grade brain tumors. Neuro-Oncology Pract [Internet]. 2015 Sep [cited 2017 Jan 26];2(3):127–36. Available from: http://nop.oxfordjournals.org/lookup/doi/10.1093/nop/npv010

128. Zuccoli G, Marcello N, Pisanello A, Servadei F, Vaccaro S, Mukherjee P, et al. Metabolic management of glioblastoma multiforme using standard therapy together with a restricted ketogenic diet: Case Report. Nutr Metab (Lond) [Internet]. 2010 [cited 2017 Jan 25];7(33):1–7. Available from: http://nutritionandmetabolism.biomedcentral.com/articles/10.1186/1743-7075-7-33

129. Institute of Health Economics. Quality Appraisal of Case Series Studies Checklist [Internet]. 2014 [cited 2017 Jan 23]. Available from: http://www.ihe.ca/research-programs/rmd/cssqac/cssqac-about

130. Klein P. Ketogenic Diet as Adjunctive Treatment in Refractory/End-stage Glioblastoma Multiforme: a Pilot Study [Internet]. 2016 [cited 2017 Mar 30]. Available from: https://clinicaltrials.gov/ct2/show/NCT01865162?term=ketogenic+diet+and+GBM&rank=1

131. Song L. Ketogenic Diet Adjunctive to Salvage Chemotherapy for Recurrent Glioblastoma:a Pilot Study (KGDinrGBM) [Internet]. 2016 [cited 2017 Apr 4]. Available from: https://clinicaltrials.gov/ct2/show/NCT02939378?term=ketogenic+diet+and+gbm&rank=2

132. Klein P. Ketogenic Diet Treatment Adjunctive to Radiation and Chemotherapy in Glioblastoma Multiforme: a Pilot Study (GBMXRT) [Internet]. 2014 [cited 2017 Apr 4]. Available from: https://clinicaltrials.gov/ct2/show/NCT02302235?term=ketogenic+diet+and+gbm&rank=3

133. Scheck A. Ketogenic diet with radiation and chemotherapy for newly diagnosed glioblastoma [Internet]. 2014 [cited 2017 Apr 4]. Available from: https://clinicaltrials.gov/ct2/show/study?term=ketogenic+diet+and+gbm&rank=4

134. Rieger J, Steinbach J. Calorie-restricted, Ketogenic Diet and Transient Fasting During Reirradiation for Patients With Recurrent Glioblastoma - Full Text View - ClinicalTrials.gov [Internet]. 2012 [cited 2017 Apr 4]. Available from: https://clinicaltrials.gov/ct2/show/study?term=ketogenic+diet+and+gbm&rank=6

135. Martin KJ, Jenkinson MD. Ketogenic Diets as an Adjuvant Therapy in Glioblastoma (KEATING) [Internet]. 2017 [cited 2017 Apr 4]. Available from: https://clinicaltrials.gov/ct2/show/study?term=ketogenic+diet+and+gbm&rank=7

136. Schwartz K. Pilot study of a metabolic nutritional therapy for the management of primary brain tumours (KETONES) [Internet]. 2012 [cited 2017 Apr 4]. Available from: https://clinicaltrials.gov/ct2/show/study?term=ketogenic+diet+and+gbm&rank=8

137. Vaisman N. The Effect of Ketogenic Diet on Malignant Tumors- Recurrence and Progress [Internet]. 2010 [cited 2017 Apr 6]. Available from: https://clinicaltrials.gov/ct2/show?term=ketogenic+diet+and+GBM&rank=9

138. Strowd R. Glioma Modified Atkins-based Diet in Patients With Glioblastoma [Internet]. 2014 [cited 2017 Apr 6]. Available from: https://clinicaltrials.gov/ct2/show?term=ketogenic+diet+and+GBM&rank=10

139. Ghodsi SM. Therapeutic effect of ketogenic diet on survival and quality of patients

with Glioblastoma Multiforme [Internet]. 2012 [cited 2017 Apr 6]. Available from: http://apps.who.int/trialsearch/Trial2.aspx?TrialID=IRCT201204099417N1

140. Jameson M. Pilot study evaluating progression-free survival in patients using a ketogenic diet while receiving chemoradiation for glioblastoma multiforme [Internet]. 2014 [cited 2017 Apr 6]. Available from: http://apps.who.int/trialsearch/Trial2.aspx?TrialID=ACTRN12614001056684

141. Guimaraes Santos J, Pereira da Fonseca CO. Ketogenic diet combined with intranasal administration of perillyl alcohol: strategy therapy to refractory Glioblastoma Multiforme to standard treatment [Internet]. 2016 [cited 2017 Apr 13]. Available from: http://apps.who.int/trialsearch/Trial2.aspx?TrialID=RBR-8x8fd9

142. Moga C, Guo B, Harstall C. Development of a Quality Appraisal Tool for Case Series Studies Using a Modified Delphi Technique. IHE Publ [Internet]. 2012;(March):1–71. Available from: http://www.ihe.ca/publications/development-of-a-quality-appraisal-tool-for-case-series-studies-using-a-modified-delphi-technique

143. INVOLVE. Why involve members of the public in research? [Internet]. 2019 [cited 2019 Jan 15]. Available from: http://www.invo.org.uk/posttyperesource/why-should-members-of-the-public-be-involved-in-research/

144. Brett J, Staniszewska S, Mockford C, Herron-Marx S, Hughes J, Tysall C, et al. Mapping the impact of patient and public involvement on health and social care research: a systematic review. Heal Expect [Internet]. 2014 Oct 1 [cited 2019 Jan 15];17(5):637–50. Available from: http://doi.wiley.com/10.1111/j.1369-7625.2012.00795.x

145. Wood S. Ketogenic therapy for adults with refractory epilpesy: Time it was on the menu for adults. Network Health Digest [Internet]. 2015;28–33. Available from: https://issuu.com/nhpublishingltd/docs/issue_106_app_file

146. Meidenbauer JJ, Mukherjee P, Seyfried TN. The glucose ketone index calculator: a simple tool to monitor therapeutic efficacy for metabolic management of brain cancer. 2015 [cited 2017 Jan 25];12. Available from: http://www.nutritionandmetabolism.com/content/12/1/12

147. Elia M. Artificial nutrition support. Med Int. 1990;82:3392–6.

148. World Health Organisation, Food and Agriculture Organization of the United Nations, United Nations University. Protein and amino acid requirements in human nutrition [Internet]. WHO. World Health Organization; 2007 [cited 2017 Aug 8]. Available from: http://www.who.int/nutrition/publications/nutrientrequirements/WHO_TRS_935/en/

149. Zupec-Kania BA, Spellman E. An Overview of the Ketogenic Diet for Pediatric Epilepsy. Nutr Clin Pract [Internet]. 2008 Dec [cited 2017 Aug 16];23(6):589–96. Available from: http://www.ncbi.nlm.nih.gov/pubmed/19033218

150. Mukherjee P, El-Abbadi MM, Kasperzyk JL, Ranes MK, Seyfried TN. Dietary restriction reduces angiogenesis and growth in an orthotopic mouse brain tumour model. Br J Cancer [Internet]. 2002 May 20 [cited 2017 Jul 19];86(10):1615–21. Available from: http://www.ncbi.nlm.nih.gov/pubmed/12085212

151. Jiang Y-S, Wang F-R. Caloric restriction reduces edema and prolongs survival in a

mouse glioma model. J Neurooncol [Internet]. 2013 Aug 24 [cited 2017 Feb 10];114(1):25–32. Available from: http://www.ncbi.nlm.nih.gov/pubmed/23703297

152. Kossoff EH, McGrogan JR, Bluml RM, Pillas DJ, Rubenstein JE, Vining EP. A Modified Atkins Diet Is Effective for the Treatment of Intractable Pediatric Epilepsy. Epilepsia [Internet]. 2006 Feb [cited 2017 Feb 10];47(2):421–4. Available from: http://www.ncbi.nlm.nih.gov/pubmed/16499770

153. Bergqvist C, Schall J, Gallagher P, Cnaan A, Stallings V. Fasting versus Gradual Initiation of the Ketogenic Diet: A Prospective, Randomized Clinical Trial of Efficacy. Epilepsia [Internet]. 2005 Nov [cited 2017 Apr 25];46(11):1810–9. Available from: http://www.ncbi.nlm.nih.gov/pubmed/16302862

154. Gerich JE, Charles MA, Grodsk GM. Regulation of pancreatic insulin and glucagon secretion. Annu Rev Physiol [Internet]. 1976 [cited 2017 Aug 2];38:353–88. Available from: http://www.annualreviews.org/doi/pdf/10.1146/annurev.ph.38.030176.002033

155. Fitzsimmons G, Sewell M. Ketogenic Diets. In: Shaw V, editor. Clinical Paediatric Dietetics. 4th Ed. Chichester, UK: John Wiley & Sons, Ltd; 2014. p. 254–380.

156. Kelley K, Clark B, Brown V, Sitzia J. Good practice in the conduct and reporting of survey research. Int J Qual Heal Care [Internet]. 2003 [cited 2019 Jan 14];15(3):261–6. Available from: https://watermark.silverchair.com/mzg031.pdf?token=AQECAHi208BE49Ooan9kkhW_Ercy7Dm3ZL_9Cf3qfKAc485ysgAAAlswggJXBgkqhkiG9w0BBwagggJIMIICRAIBADCCAj0GCSqGSIb3DQEHATAeBglghkgBZQMEAS4wEQQM2kwOkHc2nTw8niHQAgEQgIICDiwDidS7t-vQAhcrjC_Y_5QR6oJVJbgB4RVK57Vsa6CvzvD-

157. Sørensen JB, Klee M, Palshof T, Hansen HH. Performance status assessment in cancer patients. An inter-observer variability study. Br J Cancer [Internet]. 1993 Apr [cited 2017 Feb 13];67(4):773–5. Available from: http://www.ncbi.nlm.nih.gov/pubmed/8471434

158. Louis DN, Ohgaki H, Wiestler OD, Cavenee WK, Burger PC, Jouvet A, et al. The 2007 WHO classification of tumours of the central nervous system. Acta Neuropathol [Internet]. 2007 Aug [cited 2017 Jun 23];114(2):97–109. Available from: http://www.ncbi.nlm.nih.gov/pubmed/17618441

159. de Kinderen RJA, Lambrechts DAJE, Wijnen BFM, Postulart D, Aldenkamp AP, Majoie MHJM, et al. An economic evaluation of the ketogenic diet versus care as usual in children and adolescents with intractable epilepsy: An interim analysis. Epilepsia [Internet]. 2016 Jan 1 [cited 2019 Jan 31];57(1):41–50. Available from: http://doi.wiley.com/10.1111/epi.13254

160. Kossoff EH, Rowley H, Sinha SR, Vining EPG. A Prospective Study of the Modified Atkins Diet for Intractable Epilepsy in Adults. Epilepsia [Internet]. 2008 Feb [cited 2017 Apr 25];49(2):316–9. Available from: http://www.ncbi.nlm.nih.gov/pubmed/17919301

161. El-Rashidy OF, Nassar MF, Abdel-Hamid IA, Shatla RH, Abdel-Hamid MH, Gabr SS, et al. Modified Atkins diet vs classic ketogenic formula in intractable epilepsy. Acta Neurol Scand [Internet]. 2013 Dec [cited 2017 Apr 25];128(6):402–8. Available from: http://www.ncbi.nlm.nih.gov/pubmed/23679058

162. Sharma S, Sankhyan N, Gulati S, Agarwala A. Use of the modified Atkins diet for

treatment of refractory childhood epilepsy: A randomized controlled trial. Epilepsia [Internet]. 2013 Mar [cited 2017 Apr 25];54(3):481–6. Available from: http://doi.wiley.com/10.1111/epi.12069

163. Kwiterovich, Jr PO, Vining EPG, Pyzik Ps, Skolasky, Jr R, Freeman JM. Effect of a High-Fat Ketogenic Diet on Plasma Levels of Lipids, Lipoproteins, and Apolipoproteins in Children. JAMA [Internet]. 2003 Aug 20 [cited 2017 Apr 25];290(7):912. Available from: http://jama.jamanetwork.com/article.aspx?doi=10.1001/jama.290.7.912

164. Abdelwahab MG, Fenton KE, Preul MC, Rho JM, Lynch A, Stafford P, et al. The Ketogenic Diet Is an Effective Adjuvant to Radiation Therapy for the Treatment of Malignant Glioma. Canoll P, editor. PLoS One [Internet]. 2012 May 1 [cited 2017 Feb 14];7(5):e36197. Available from: http://dx.plos.org/10.1371/journal.pone.0036197

165. Allen BG, Bhatia SK, Buatti JM, Brandt KE, Lindholm KE, Button AM, et al. Ketogenic diets enhance oxidative stress and radio-chemo-therapy responses in lung cancer xenografts. Clin Cancer Res. 2013;19(14).

166. National Institute for Health and Care Excellent (NICE). Brain tumours (primary) and brain metastases in adults (NG99) [Internet]. NICE; 2018 [cited 2019 Jan 2]. Available from: https://www.nice.org.uk/guidance/ng99/chapter/Recommendations#investigation-of-suspected-glioma

167. Strowd RE, Grossman SA. The Role of Glucose Modulation and Dietary Supplementation in Patients With Central Nervous System Tumors. Curr Treat Options Oncol [Internet]. 2015 Aug 5 [cited 2016 Nov 15];16(8):36. Available from: http://link.springer.com/10.1007/s11864-015-0356-2

168. Eldridge SM, Chan CL, Campbell MJ, Bond CM, Hopewell S, Thabane L, et al. CONSORT 2010 statement: Extension to randomised pilot and feasibility trials. BMJ. 2016;355.

169. Martin-McGill KJ, Marson AG, Tudur Smith C, Jenkinson MD. The Modified Ketogenic Diet in Adults with Glioblastoma: An Evaluation of Feasibility and Deliverability within the National Health Service. Nutr Cancer [Internet]. 2018 May 19 [cited 2018 Jul 10];70(4):643–9. Available from: http://www.ncbi.nlm.nih.gov/pubmed/29668317

170. National Institute for Health Research. Feasibility and Pilot studies [Internet]. 2019 [cited 2019 Mar 6]. Available from: https://www.nihr.ac.uk/funding-and-support/documents/funding-for-research-studies/research-programmes/PGfAR/Feasibility and Pilot studies.pdf

171. Craig P, Dieppe P, Macintyre S, Michie S, Nazareth I, Petticrew M. Developing and evaluating complex interventions: the new Medical Research Council guidance. BMJ [Internet]. 2008 Sep 29 [cited 2019 Jan 21];337:a1655. Available from: https://www.bmj.com/content/337/bmj.a1655

172. Avery KNL, Williamson PR, Gamble C, O'Connell Francischetto E, Metcalfe C, Davidson P, et al. Informing efficient randomised controlled trials: exploration of challenges in developing progression criteria for internal pilot studies. BMJ Open [Internet]. 2017 Feb 17 [cited 2018 Jan 5];7(2):e013537. Available from: http://www.ncbi.nlm.nih.gov/pubmed/28213598

173. Unger JM, Cook E, Tai E, Bleyer A. The Role of Clinical Trial Participation in Cancer

Research: Barriers, Evidence, and Strategies. Am Soc Clin Oncol Educ B [Internet]. 2016 [cited 2018 Jul 31];36:185–98. Available from: http://www.ncbi.nlm.nih.gov/pubmed/27249699

174. Mills EJ, Seely D, Rachlis B, Griffith L, Wu P, Wilson K, et al. Barriers to participation in clinical trials of cancer: a meta-analysis and systematic review of patient-reported factors. Lancet Oncol. 2006;7(2):141–8.

175. Manne S, Kashy D, Albrecht T, Wong Y-N, Lederman Flamm A, Benson AB, et al. Attitudinal barriers to participation in oncological clinical trials: factor analysis and correlates of barriers. Eur J Cancer Care (Engl). 2015;24(1):28–38.

176. Wright JR, Crooks D, Ellis PM, Mings D, Whelan TJ. Factors that influence the recruitment of patients to phase III studies in oncology: The perspective of the clinical research associate. Cancer. 2002;95(7):1584–91.

177. McDonald AM, Knight RC, Campbell MK, Entwistle VA, Grant AM, Cook JA, et al. What influences recruitment to randomised controlled trials? A review of trials funded by two UK funding agencies. Trials [Internet]. 2006 Apr 7 [cited 2018 Jul 10];7:9. Available from: http://www.ncbi.nlm.nih.gov/pubmed/16603070

178. Walters SJ, Bonacho I, Henriques-Cadby A, Bortolami O, Flight L, Hind D, et al. Recruitment and retention of participants in randomised controlled trials: a review of trials funded and published by the United Kingdom Health Technology Assessment Programme. BMJ Open [Internet]. 2017 [cited 2018 Jun 11];7. Available from: http://dx.doi.org/10.1136/

179. Daykin A, Clement C, Gamble C, Kearney A, Blazeby J, Clarke M, et al. “Recruitment, recruitment, recruitment” - the need for more focus on retention: a qualitative study of five trials. Trials [Internet]. 2018 Jan 29 [cited 2019 Mar 6];19(1):76. Available from: http://www.ncbi.nlm.nih.gov/pubmed/29378618

180. Chhatre S, Jefferson A, Cook R, Meeker CR, Kim JH, Hartz KM, et al. Patient-centered recruitment and retention for a randomized controlled study. Trials [Internet]. 2018 Dec 27 [cited 2019 Mar 6];19(1):205. Available from: https://trialsjournal.biomedcentral.com/articles/10.1186/s13063-018-2578-7

181. Ariail K, Watts C (Cindy), Bowen DJ. Retention in a Breast Cancer Risk Information Trial: Motivations of a Population-Based Sample of Women. Heal Educ Behav [Internet]. 2006 Oct 31 [cited 2019 Mar 6];33(5):591–603. Available from: http://www.ncbi.nlm.nih.gov/pubmed/16861591

182. Stow R, Rushton A, Ives N, Smith C, Rick C. A cluster randomised feasibility trial evaluating six-month nutritional interventions in the treatment of malnutrition in care home-dwelling adults: Recruitment, data collection and protocol. Pilot Feasibility Stud. 2015;1(1):1–14.

183. Stradling C, Thomas GN, Hemming K, Frost G, Garcia-Perez I, Redwood S, et al. Randomised controlled pilot study to assess the feasibility of a Mediterranean Portfolio dietary intervention for cardiovascular risk reduction in HIV dyslipidaemia: A study protocol. BMJ Open. 2016;6(2):1–12.

184. Beck S a, Tisdale MJ. Effect of insulin on weight loss and tumour growth in a cachexia model. Br J Cancer [Internet]. 1989;59(5):677–81. Available from: http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=2247211&tool=pmcentrez&rendertype=abstract

185. Fearon KC, Borland W, Preston T, Tisdale MJ, Shenkin A, Calman KC. Cancer cachexia: influence of systemic ketosis on substrate levels and nitrogen metabolism. Am J Clin Nutr [Internet]. 1988 Jan [cited 2017 Jul 20];47(1):42–8. Available from: http://www.ncbi.nlm.nih.gov/pubmed/3122552

186. Fearon KCH, Borland W, Preston T, Tisdale MJ, Shenkin A, Calman KC. Cancer cachexia: Influence of systemic ketosis on substrate levels and nitrogen metabolism. Am J Clin Nutr. 1988;47(1):42–8.

187. Neal EG, Chaffe H, Schwartz RH, Lawson MS, Edwards N, Fitzsimmons G, et al. A randomized trial of classical and medium-chain triglyceride ketogenic diets in the treatment of childhood epilepsy. Epilepsia [Internet]. 2009 May [cited 2017 Feb 10];50(5):1109–17. Available from: http://www.ncbi.nlm.nih.gov/pubmed/19054400

188. Huttenlocher PR, Wilbourn AJ, Signore JM. Medium-chain triglycerides as a therapy for intractable childhood epilepsy. Neurology [Internet]. 1971 Nov [cited 2017 Feb 10];21(11):1097–103. Available from: http://www.ncbi.nlm.nih.gov/pubmed/5166216

189. Schwartz RH, Eaton J, Bower BD, Aynsley-Green A. Ketogenic diets in the treatment of epilepsy: short-term clinical effects. Dev Med Child Neurol [Internet]. 1989 Apr [cited 2017 Aug 1];31(2):145–51. Available from: http://www.ncbi.nlm.nih.gov/pubmed/2786822

190. Lord K, Magrath G. Use of the ketogenic diet and dietary practices in the UK. J Hum Nutr Diet [Internet]. 2010 Apr [cited 2017 Aug 1];23(2):126–32. Available from: http://www.ncbi.nlm.nih.gov/pubmed/20487177

191. Bergqvist AGC, Schall JI, Gallagher PR, Cnaan A, Stallings VA. Fasting versus Gradual Initiation of the Ketogenic Diet: A Prospective, Randomized Clinical Trial of Efficacy. Epilepsia [Internet]. 2005 Nov [cited 2017 Feb 10];46(11):1810–9. Available from: http://www.ncbi.nlm.nih.gov/pubmed/16302862

192. American Society for Parenteral and Enteral Nutrition. Guidelines for the use of parenteral and enteral nutrition in adult and pediatric patients. J Parenter Enter Nutr. 2002;26(Supplement 1).

193. Barak N, Wall-Alonso E, Sitrin M. Evaluation of stress factors and body weight adjustments currently used to estimate energy expenditure in hospitalized patients. J Parenter Enter Nutr [Internet]. 2002 Jul [cited 2017 Feb 13];26(4):231–8. Available from: http://www.ncbi.nlm.nih.gov/pubmed/12090688

194. Department of Health. Dietary reference values for food energy and nutrients for the United Kingdom. H.M.S.O; 1991. 210 p.

195. Henry CJK. Basal metabolic rate studies in humans: measurement and development of new equations. Public Health Nutr [Internet]. 2005 Oct [cited 2017 Feb 13];8(7A):1133–52. Available from: http://www.ncbi.nlm.nih.gov/pubmed/16277825

196. Hyltander A, Drott C, Körner U, Sandström R, Lundholm K. Elevated energy expenditure in cancer patients with solid tumours. Eur J Cancer Clin Oncol [Internet]. 1991 Jan [cited 2017 Feb 13];27(1):9–15. Available from: http://linkinghub.elsevier.com/retrieve/pii/027753799190050N

197. Knox LS, Crosby LO, Feurer ID, Buzby GP, Miller CL, Mullen JL. Energy expenditure in malnourished cancer patients. Ann Surg [Internet]. 1983 Feb [cited 2017 Feb 13];197(2):152–62. Available from: http://www.ncbi.nlm.nih.gov/pubmed/6824369

198. Todorovic V, Micklewright A. A Pocket Guide To Clinical Nutrition [Internet]. 4th ed. Birmingham: The Parenteral and Enteral Nutrition Group of the British Dietetic Association; 2011 [cited 2017 Feb 13]. Available from: http://www.peng.org.uk/publications-resources/pocket-guide.php

199. Livesey G, Elia M. Estimation of energy expenditure, net carbohydrate utilization, and net fat oxidation and synthesis by indirect calorimetry: evaluation of errors with special reference to the detailed composition of fuels. Am J Clin Nutr [Internet]. 1988 Apr [cited 2017 Aug 17];47(4):608–28. Available from: http://www.ncbi.nlm.nih.gov/pubmed/3281434

200. Jenkinson M. Walton Centre / Clatterbridge Centre for Oncology guidelines for high grade glioma management [Internet]. Merseyside and Cheshire Neuro-Oncology Clinical Network Group. Liverpool, UK; 2011 [cited 2017 Feb 13]. Available from: http://www.nwcscnsenate.nhs.uk/files/7114/1232/7814/High_grade_glioma_guidelines_November_2013.pdf

201. Barnard ND, Gloede L, Cohen J, Jenkins DJA, Turner-McGrievy G, Green AA, et al. A low-fat vegan diet elicits greater macronutrient changes, but is comparable in adherence and acceptability, compared with a more conventional diabetes diet among individuals with type 2 diabetes. J Am Diet Assoc [Internet]. 2009;109(2):263–72. Available from: http://dx.doi.org/10.1016/j.jada.2008.10.049

202. Shanyinde M, Pickering RM, Weatherall M. Questions asked and answered in pilot and feasibility randomized controlled trials. BMC Med Res Methodol. 2011;11:117.

203. Bugge C, Williams B, Hagen S, Logan J, Glazener C, Pringle S, et al. A process for Decision-making after Pilot and feasibility Trials (ADePT): development following a feasibility study of a complex intervention for pelvic organ prolapse. Trials [Internet]. 2013;14(1):353. Available from: http://www.trialsjournal.com/content/14/1/353

204. Billingham SA, Whitehead AL, Julious SA. An audit of sample sizes for pilot and feasibility trials being undertaken in the United Kingdom registered in the United Kingdom Clinical Research Network database. BMC Med Res Methodol [Internet]. 2013 Dec 20 [cited 2017 Feb 13];13(1):104. Available from: http://www.ncbi.nlm.nih.gov/pubmed/23961782

205. Hertzog MA. Considerations in determining sample size for pilot studies. Res Nurs Health [Internet]. 2008 Apr [cited 2017 Feb 13];31(2):180–91. Available from: http://www.ncbi.nlm.nih.gov/pubmed/18183564

206. Hooper R. Justifying sample size for a feasibility study. London;

207. Wen PY, Macdonald DR, Reardon DA, Cloughesy TF, Sorensen AG, Galanis E, et al. Updated Response Assessment Criteria for High-Grade Gliomas: Response Assessment in Neuro-Oncology Working Group. J Clin Oncol [Internet]. 2010 Apr 10 [cited 2017 Feb 13];28(11):1963–72. Available from: http://www.ncbi.nlm.nih.gov/pubmed/20231676

208. European Organisation for Research and Treatment of Cancer (EORTC). EORTC QLQ-C30 Scoring Manual The EORTC QLQ-C30 [Internet]. 2001 [cited 2019 Jul 29]. Available from: https://www.eortc.org/app/uploads/sites/2/2018/02/SCmanual.pdf

209. Delahanty LM, Riggs M, Klioze SS, Chew RD, England RD, Digenio A. Maximizing retention in long-term clinical trials of a weight loss agent: use of a dietitian support team. Obes Sci Pract [Internet]. 2016 Sep 1 [cited 2019 Mar 11];2(3):256–65. Available from: http://doi.wiley.com/10.1002/osp4.57

210. Schmidt M, Pfetzer N, Schwab M, Strauss I, Kämmerer U. Effects of a ketogenic diet on the quality of life in 16 patients with advanced cancer: A pilot trial. Nutr Metab (Lond) [Internet]. 2011;8(1):54. Available from: http://nutritionandmetabolism.biomedcentral.com/articles/10.1186/1743-7075-8-54

211. Stryker JE, Wray RJ, Emmons KM, Winer E, Demetri G. Understanding the decisions of cancer clinical trial participants to enter research studies: Factors associated with informed consent, patient satisfaction, and decisional regret. Patient Educ Couns [Internet]. 2006 Oct [cited 2018 Aug 17];63(1–2):104–9. Available from: http://www.ncbi.nlm.nih.gov/pubmed/16242898

212. Albrecht TL, Eggly SS, Gleason MEJ, Harper FWK, Tanina S, Peterson AM, et al. Influence of clinical communication on patients' decisoin making on participation in clinical trials. J Clin Oncol. 2013;26(16):1–15.

213. Jenkinson MD, Javadpour M, Haylock BJ, Young B, Gillard H, Vinten J, et al. The ROAM/EORTC-1308 trial: Radiation versus Observation following surgical resection of Atypical Meningioma: study protocol for a randomised controlled trial. Trials [Internet]. 2015 Dec 14 [cited 2019 Mar 11];16(1):519. Available from: http://trialsjournal.biomedcentral.com/articles/10.1186/s13063-015-1040-3

214. Huang GD, Bull J, Johnston McKee K, Mahon E, Harper B, Roberts JN. Clinical trials recruitment planning: A proposed framework from the Clinical Trials Transformation Initiative. Contemp Clin Trials [Internet]. 2018 Mar 1 [cited 2019 Mar 11];66:74–9. Available from: https://www.sciencedirect.com/science/article/pii/S155171441730753X

215. Paramasivan S, Huddart R, Hall E, Lewis R, Birtle A, Donovan JL. Key issues in recruitment to randomised controlled trials with very different interventions: a qualitative investigation of recruitment to the SPARE trial (CRUK/07/011). Trials. 2011;12:1–15.

216. Sherlock A, Brownie S. Patients' recollection and understanding of informed consent: A literature review. ANZ J Surg. 2014;84(4):207–10.

217. Treweek S, Lockhart P, Pitkethly M, Cook JA, Kjeldstrøm M, Johansen M, et al. Methods to improve recruitment to randomised controlled trials: Cochrane systematic review and meta-analysis. BMJ Open. 2013;3(2).

218. Downer SM, Cody MM, McCluskey P, Wilson PD, Arnott SJ, Lister TA, et al. Pursuit and practice of complementary therapies by cancer patients receiving conventional treatment. BMJ [Internet]. 1994 Jul 9 [cited 2019 Mar 11];309(6947):86–9. Available from: http://www.ncbi.nlm.nih.gov/pubmed/8038672

219. Meidenbauer JJ, Mukherjee P, Seyfried TN. The glucose ketone index calculator: a simple tool to monitor therapeutic e...: EBSCOhost. Nutr Metab [Internet]. 2015 [cited 2017 Jan 25];12(12):1–7. Available from: http://web.a.ebscohost.com.liverpool.idm.oclc.org/ehost/pdfviewer/pdfviewer?vid=15&sid=0fe16254-8549-4478-a717-36c8c7055bbf%40sessionmgr4008&hid=4212

220. van Delft R, Lambrechts D, Verschuure P, Hulsman J, Majoie M. Blood beta-hydroxybutyrate correlates better with seizure reduction due to ketogenic diet than do ketones in the urine. Seizure [Internet]. 2010 Jan 1 [cited 2019 Mar 13];19(1):36–9. Available from: https://www.sciencedirect.com/science/article/pii/S1059131109002143

221. Gilbert DL, Pyzik PL, Freeman JM. The Ketogenic Diet: Seizure Control Correlates Better With Serum β-Hydroxybutyrate Than With Urine Ketones. J Child Neurol [Internet]. 2000 Dec 2 [cited 2019 Mar 13];15(12):787–90. Available from: http://journals.sagepub.com/doi/10.1177/088307380001501203

222. Driscoll KA, Killian M, Johnson SB, Silverstein JH, Deeb LC. Predictors of study completion and withdrawal in a randomized clinical trial of a pediatric diabetes adherence intervention. Contemp Clin Trials [Internet]. 2009 May [cited 2019 Mar 13];30(3):212–20. Available from: http://www.ncbi.nlm.nih.gov/pubmed/19470311

223. Osoba D, Brada M, Prados MD, Yung WKA. Effect of disease burden on health-related quality of life in patients with malignant gliomas. Neuro Oncol [Internet]. 2000 Oct 1 [cited 2019 Mar 22];2(4):221–8. Available from: http://academic.oup.com/neuro-oncology/article/2/4/221/1059698/Effect-of-disease-burden-on-healthrelated-quality

224. Sacks FM, Lichtenstein AH, Wu JHY, Appel LJ, Creager MA, Kris-Etherton PM, et al. Dietary Fats and Cardiovascular Disease: A Presidential Advisory From the American Heart Association. Circulation [Internet]. 2017 Jul 18 [cited 2019 Mar 13];136(3). Available from: https://www.ahajournals.org/doi/10.1161/CIR.0000000000000510

225. Dehghan M, Mente A, Zhang X, Swaminathan S, Li W, Mohan V, et al. Associations of fats and carbohydrate intake with cardiovascular disease and mortality in 18 countries from five continents (PURE): a prospective cohort study. Lancet [Internet]. 2017 Nov 4 [cited 2019 Mar 13];390(10107):2050–62. Available from: http://www.ncbi.nlm.nih.gov/pubmed/28864332

226. National Institute for Health and Care Excellence. Cardiovascular disease: risk assessment and reduction, including lipid modification. Clinical guideline [CG181]. 2016 [cited 2019 Mar 13]; Available from: https://www.nice.org.uk/guidance/cg181

227. Hebert JR, Ma Y, Clemow L, Ockene IS, Saperia G, Stanek EJ, et al. Gender Differences in Social Desirability and Social Approval Bias in Dietary Self-report. Am J Epidemiol [Internet]. 1997 Dec 15 [cited 2019 Mar 13];146(12):1046–55. Available from: https://academic.oup.com/aje/article-lookup/doi/10.1093/oxfordjournals.aje.a009233

228. O'Brien BC, Harris IB, Beckman TJ, Reed DA, Cook DA. Standards for Reporting Qualitative Research: A Synthesis of Recommendations. Acad Med [Internet]. 2014 [cited 2019 Mar 8];89(9):0–00. Available from: http://links.lww.com/ACADMED/A218.

229. Gillies K, Skea Z, Politi MC, Brehaut JC. Decision support interventions for people making decisions about participation in clinical trials. In: Gillies K, editor. Cochrane Database of Systematic Reviews [Internet]. Chichester, UK: John Wiley & Sons, Ltd; 2012 [cited 2018 Aug 7]. Available from: http://doi.wiley.com/10.1002/14651858.CD009736

230. Barry MJ, Edgman-levitan S, Billingham V. Shared Decision Making — The Pinnacle of Patient-Centered Care. N Engl J Med. 2012;366(9):780–1.

231. Brom L, Pasman HRW, Widdershoven GAM, van der Vorst MJDL, Reijneveld JC, Postma TJ, et al. Patients' preferences for participation in treatment decision-making at the end of life: qualitative interviews with advanced cancer patients. PLoS One [Internet]. 2014;9(6):e100435. Available from: http://www.ncbi.nlm.nih.gov/pubmed/24964036%5Cnhttp://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=PMC4070976

232. NHS England. Shared decision making [Internet]. 2018 [cited 2018 Aug 6]. Available from: https://www.england.nhs.uk/shared-decision-making/

233. Reyna VF. Theories of medical decision making and health: An evidence based approach. Med Decis Mak. 2008;28(6):829–33.

234. Ubel P. Beyond costs and benefits: Understanding how patients make health care decisions. Oncologist [Internet]. 2010;15(suppl 1):5–10. Available from: http://theoncologist.alphamedpress.org/content/15/suppl_1/5.short

235. Ells C, Hunt MR, Chambers-Evans J. Relational autonomy as an essential component of patient-centered care. Int J Fem Approaches to Bioeth. 2011;4(2):79–101.

236. Gillies K, Elwyn G, Cook J. Making a decision about trial participation: the feasibility of measuring deliberation during the informed consent process for clinical trials. Trials [Internet]. 2014 Dec 30 [cited 2018 Aug 7];15(1):307. Available from: http://trialsjournal.biomedcentral.com/articles/10.1186/1745-6215-15-307

237. Cancer Research UK. Breast cancer survival statistics [Internet]. 2018 [cited 2018 Aug 6]. Available from: https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/breast-cancer/survival

238. Cancer Research UK. Prostate cancer survival statistics [Internet]. 2018 [cited 2018 Aug 6]. Available from: https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/prostate-cancer/survival

239. The Brain Tumour Charity. Brain tumour prognosis [Internet]. 2018 [cited 2018 Aug 6]. Available from: https://www.thebraintumourcharity.org/understanding-brain-tumours/getting-a-diagnosis/prognosis/prognosis-specific-brain-tumours/

240. Cherry MG, Smith H, Perkins E, Boland A. Reviewing Qualitative Evidence. In: Boland A, Cherry MG, Dickson R, editors. Doing a Systematic Review: A student's guide [Internet]. 2nd ed. London: SAGE Publications Ltd; 2017 [cited 2018 Aug 31]. p. 194–221. Available from: https://uk.sagepub.com/en-gb/eur/node/58991/print

241. Huizinga GA, Sleijfer DT, van de Wiel HB, van der Graaf WT. Decision-making process in patients before entering phase III cancer clinical trials: a pilot study. Cancer Nurs [Internet]. 1999 Apr [cited 2018 Aug 7];22(2):119–25. Available from: http://www.ncbi.nlm.nih.gov/pubmed/10217027

242. Madsen SM, Holm S, Riis P. Attitudes towards clinical research among cancer trial participants and non-participants: An interview study using a grounded theory approach. J Med Ethics. 2007;33(4):234–40.

243. Madsen SM, Holm S, Riis P. Participating in a cancer clinical trial? The balancing of options in the loneliness of autonomy: A grounded theory interview study. Acta Oncol (Madr) [Internet]. 2007 [cited 2018 Aug 8];46:49–59. Available from: https://web-b-ebscohost-com.liverpool.idm.oclc.org/ehost/pdfviewer/pdfviewer?vid=1&sid=8b7e8bb7-49f0-

4faf-bd45-f471190bf1fe%40sessionmgr104

244. Godskesen T, Nygren P, Nordin K, Hansson M, Kihlbom U. Phase 1 clinical trials in end-stage cancer: Patient understanding of trial premises and motives for participation. Support Care Cancer. 2013;21(11):3137–42.

245. Reeder-Hayes KE, Roberts MC, Henderson GE, Dees EC. Informed Consent and Decision Making Among Participants in Novel-Design Phase I Oncology Trials. J Oncol Pract [Internet]. 2017;13(10):e863–73. Available from: http://ascopubs.org/doi/10.1200/JOP.2017.021303

246. Naik AD, Street RL, Castillo D, Abraham NS, Abraham NS. Health literacy and decision making styles for complex antithrombotic therapy among older multimorbid adults. Patient Educ Couns [Internet]. 2011 Dec [cited 2018 Aug 7];85(3):499–504. Available from: http://www.ncbi.nlm.nih.gov/pubmed/21251788

247. Smith SK, Dixon A, Trevena L, Nutbeam D, McCaffery KJ. Exploring patient involvement in healthcare decision making across different education and functional health literacy groups. Soc Sci Med [Internet]. 2009 Dec 1 [cited 2018 Aug 7];69(12):1805–12. Available from: https://www.sciencedirect.com/science/article/pii/S0277953609006601

248. Paasche-Orlow MK, Wolf MS. The Causal Pathways Linking Health Literacy to Health Outcomes. Am J Health Behav [Internet]. 2007 [cited 2018 Aug 7];31(1):s19–26. Available from: https://www.ingentaconnect.com/content/png/ajhb/2007/00000031/A00100s1/art00004

249. Parker R. Health literacy: a challenge for American patients and their health care providers. Health Promot Int [Internet]. 2000 Dec 1 [cited 2018 Aug 7];15(4):277–83. Available from: https://academic.oup.com/heapro/article-lookup/doi/10.1093/heapro/15.4.277

250. Agrawal M, Emanuel EJ. Ethics of Phase 1 Oncology Studies. JAMA [Internet]. 2003 Aug 27 [cited 2018 Aug 9];290(8):1075. Available from: http://www.ncbi.nlm.nih.gov/pubmed/12941681

251. Jansen LA, Appelbaum PS, Klein WMP, Weinstein ND, Cook W, Fogel JS, et al. Unrealistic optimism in early-phase oncology trials. IRB Ethics Hum Res. 2011;33(1):1–8.

252. Jansen LA, Mahadevan D, Appelbaum PS, Klein WMP, Weinstein ND, Mori M, et al. Dispositional optimism and therapeutic expectations in early-phase oncology trials. Cancer [Internet]. 2016 Apr 15 [cited 2018 Aug 9];122(8):1238–46. Available from: http://www.ncbi.nlm.nih.gov/pubmed/26882017

253. Miller FG, Joffe S. Phase 1 oncology trials and informed consent. 2012 [cited 2018 Aug 9]; Available from: http://jme.bmj.com/

254. McCann SK, Campbell MK, Entwistle VA. Reasons for participating in randomised controlled trials: Conditional altruism and considerations for self. Trials. 2010;11:1–10.

255. Martin-McGill KJ, Marson AG, Tudur Smith C, Jenkinson MD. Ketogenic diets as an adjuvant therapy in glioblastoma (the KEATING trial): study protocol for a randomised pilot study. Pilot Feasibility Stud [Internet]. 2017 Dec 28 [cited 2018 Jun

11];3(1):67. Available from: https://pilotfeasibilitystudies.biomedcentral.com/articles/10.1186/s40814-017-0209-9

256. Bryman A. Mixed methods research: combining quanitative and qualitative research. In: Social Research Methods. 5th ed. Oxford: Oxford University Press; 2016. p. 635–87.

257. Emmel N. Sampling and choosing cases in qualitative research : a realist approach [Internet]. 1st ed. London; 2013 [cited 2018 Nov 22]. 33-44 p. Available from: https://books.google.co.uk/books?hl=en&lr=&id=HfnAAQAAQBAJ&oi=fnd&pg=PP1&ots=dYzXBfCsuw&sig=74vSyUWZhLzCkQyjjRPd4xTBR_Y&redir_esc=y#v=onepage&q&f=false

258. Malterud K, Siersma VD, Guassora AD. Sample Size in Qualitative Interview Studies: Guided by Information Power. Qual Health Res [Internet]. 2016;26(13):1753–60. Available from: https://doi.org/10.1177/1049732315617444

259. Sim J, Saunders B, Waterfield J, Kingstone T. Can sample size in qualitative research be determined a priori? Int J Soc Res Methodol [Internet]. 2018;21(5):619–34. Available from: https://doi.org/10.1080/13645579.2018.1454643

260. Gill P, Stewart K, Treasure E, Chadwick B. Methods of data collection in qualitative research: interviews and focus groups. Br Dent J [Internet]. 2008 Mar 22 [cited 2018 Sep 3];204(6):291–5. Available from: http://www.nature.com/articles/bdj.2008.192

261. Braun V, Clarke V. Using thematic analysis in psychology. Qual Res Psychol [Internet]. 2006 [cited 2018 Sep 3];3(2):77–101. Available from: http://www.tandfonline.com/action/journalInformation?journalCode=uqrp20

262. Murphy E, Dingwall R, Greatbatch D, Parker S, Watson P. Qualitative research methods in health technology assessment: a review of the literature. Health Technol Assess [Internet]. 1998 [cited 2018 Sep 3];2(16):1–274. Available from: http://www.ncbi.nlm.nih.gov/pubmed/9919458

263. Seale C. Quality in Qualitative Research [Internet]. Vol. 5, Qualitative Inquiry. 1999 [cited 2018 Sep 3]. Available from: http://journals.sagepub.com/doi/pdf/10.1177/107780049900500402

264. Ministry of Housing C and LG. English Indices of Deprivation 2015 [Internet]. Swirrl IT Ltd. 2015 [cited 2018 Sep 3]. Available from: http://imd-by-postcode.opendatacommunities.org/

265. Welsh Government. Welsh Index of Multiple Deprivation [Internet]. Crown Copyright. 2014 [cited 2018 Sep 3]. Available from: http://wimd.wales.gov.uk/?lang=en

266. Bryman A. Social research strategies: quantitative research and qualitative research. In: Social Research Methods. 5th ed. Oxford: Oxford University Press; 2016. p. 16–38.

267. Ormston R, Spencer L, Barnard Ma, Snape D. The Foundations of Qualitative Research. In: Ritchie J, Lewis J, McNaughton Nicholls C, Ormston R, editors. Qualitative Research Practice: A Guide for Social Science Students and Researchers. 2nd ed. London: SAGE Publications Ltd; 2014. p. 1–23.

268. Bryman A. Social Research Methods. 5th ed. Oxford: Oxford University Press; 2016.

269. Ritchie J, Lewis J, McNaughton Nicholls C, Ormston R. The Foundations of Qualitative Research. In: Qualitative Research Practice: A Guide for Social Science Students and Researchers. Second Edi. London: SAGE Publications Ltd; 2014. p. 1–23.

270. Lincoln YS, Guba EG. Establishing Trustworthiness. In: Naturalistic Inquiry [Internet]. SAGE publications; 1985 [cited 2018 Sep 10]. p. 289–331. Available from: https://ethnographyworkshop.files.wordpress.com/2014/11/lincoln-guba-1985-establishing-trustworthiness-naturalistic-inquiry.pdf

271. Stiles WB. QUALITY CONTROL IN QUALITATIVE RESEARCH. Clin Psycho&y Rmiew [Internet]. 1993 [cited 2018 Sep 10];13:593–618. Available from: https://ac.els-cdn.com/027273589390048Q/1-s2.0-027273589390048Q-main.pdf?_tid=bf1d6bf7-15c8-4c7c-b3bc-f630c5899dfb&acdnat=1536585167_cd0daa60e87a11ade59e7fb2a4b5c2c7

272. Department of Communities and Local Government. The English Indices of Deprivation 2015 [Internet]. 2016 [cited 2018 Aug 23]. Available from: https://www.gov.uk/government/statistics/english-indices-of-deprivation-2015

273. Brown SL, Whiting D, Fielden HG, Saini P, Beesley H, Holcombe C, et al. Qualitative analysis of how patients decide that they want risk-reducing mastectomy, and the implications for surgeons in responding to emotionally-motivated patient requests. Gupta S, editor. PLoS One [Internet]. 2017 May 26 [cited 2018 Aug 20];12(5):e0178392. Available from: http://dx.plos.org/10.1371/journal.pone.0178392

274. Svenson O. Differentiation and consolidation theory of human decision making: A frame of reference for the study of pre- and post-decision processes. Acta Psychol (Amst) [Internet]. 1992 Aug 1 [cited 2018 Aug 20];80(1–3):143–68. Available from: https://www.sciencedirect.com/science/article/pii/000169189290044E

275. Wilkes LM, O'Baugh J, Luke S, George A. Positive attitude in cancer: patients' perspectives. Oncol Nurs Forum [Internet]. 2003;30(3):412–6. Available from: http://www.ncbi.nlm.nih.gov/pubmed/12719741

276. Miranda SP, Bernacki RE, Paladino JM, Norden AD, Kavanagh JE, Palmor MC, et al. A Descriptive Analysis of End-of-Life Conversations With Long-Term Glioblastoma Survivors. Am J Hosp Palliat Med [Internet]. 2018 May 9 [cited 2018 Jul 2];35(5):804–11. Available from: http://journals.sagepub.com/doi/10.1177/1049909117738996

277. Agrawal M, Emanuel EJ. Ethics of Phase 1 Oncology Studies. JAMA [Internet]. 2003 Aug 27 [cited 2018 Aug 20];290(8):1075. Available from: http://www.ncbi.nlm.nih.gov/pubmed/12941681

278. de Vries M, Holland RW, Witteman CLM. Fitting decisions: Mood and intuitive versus deliberative decision strategies. Cogn Emot [Internet]. 2008 Aug [cited 2018 Aug 20];22(5):931–43. Available from: http://www.tandfonline.com/doi/abs/10.1080/02699930701552580

279. Health Research Authority. Good Clinical Practice [Internet]. 2018 [cited 2019 Aug 5]. Available from: https://www.hra.nhs.uk/planning-and-improving-research/policies-standards-legislation/good-clinical-practice/

280. Lipsman N, Skanda A, Kimmelman J, Bernstein M. The attitudes of brain cancer patients and their caregivers towards death and dying: A qualitative study. BMC

Palliat Care. 2007;6:10–5.

281. Fearn P, Avenell A, McCann S, Milne AC, Maclennan G. Factors influencing the participation of older people in clinical trials- data analysis from the MAVIS trial. J Nutr Heal Ageing [Internet]. 2010 [cited 2018 Aug 17];14(1):51–6. Available from: https://link.springer.com/content/pdf/10.1007%2Fs12603-010-0009-x.pdf

282. Miller SM, Hudson S V, Egleston BL, Manne S, Buzaglo JS, Devarajan K, et al. The relationships among knowledge, self-efficacy, preparedness, decisional conflict, and decisions to participate in a cancer clinical trial. Psychooncology [Internet]. 2013 Mar [cited 2018 Aug 17];22(3):481–9. Available from: http://www.ncbi.nlm.nih.gov/pubmed/22331643

283. Gillies K, Entwistle VA. Supporting positive experiences and sustained participation in clinical trials: looking beyond information provision. J Med Ethics [Internet]. 2012 Dec 8 [cited 2018 Aug 20];38(12):751–6. Available from: http://www.ncbi.nlm.nih.gov/pubmed/22875981

284. Kendall M, Murray SA, Carduff E, Worth A, Harris F, Lloyd A, et al. Use of multiperspective qualitative interviews to understand patients' and carers' beliefs, experiences, and needs. BMJ [Internet]. 2009 Oct 14 [cited 2018 Aug 20];339:b4122. Available from: http://www.ncbi.nlm.nih.gov/pubmed/19828645

285. White C, Hardy J. What do palliative care patients and their relatives think about research in palliative care?—a systematic review. Support Care Cancer [Internet]. 2010 Aug 25 [cited 2018 Aug 20];18(8):905–11. Available from: http://www.ncbi.nlm.nih.gov/pubmed/19705165

286. Adelbratt S, Strang P. Death anxiety in brain tumour patients and their spouses. Palliat Med. 2000;14(2):499–507.

287. Frenkel M, Ari SL, Engebretson J, Peterson N, Maimon Y, Cohen L, et al. Activism among exceptional patients with cancer. Support Care Cancer. 2011;19(8):1125–32.

288. Entwistle VA, Carter SM, Cribb A, McCaffery K. Supporting patient autonomy: The importance of clinician-patient relationships. J Gen Intern Med. 2010;25(7):741–5.

289. Gillies K, Cotton SC, Brehaut JC, Politi MC, Skea Z. Decision aids for people considering taking part in clinical trials. Cochrane Database Syst Rev [Internet]. 2015 Nov 27 [cited 2018 Sep 7];(11):CD009736. Available from: http://www.ncbi.nlm.nih.gov/pubmed/26613337

290. Walters SJ, Bonacho I, Henriques-Cadby A, Bortolami O, Flight L, Hind D, et al. Recruitment and retention of participants in randomised controlled trials: a review of trials funded and published by the United Kingdom Health Technology Assessment Programme. BMJ Open [Internet]. 2017 [cited 2018 Jul 10];7:15276. Available from: http://www.isrctn.com/

291. Morgan H, Thomson G, Crossland N, Dykes F, Hoddinott P. Combining PPI with qualitative research to engage "harder-to-reach" populations: service user groups as co-applicants on a platform study for a trial. Res Involv Engagem [Internet]. 2016 Dec 24 [cited 2019 Mar 18];2(1):7. Available from: http://researchinvolvement.biomedcentral.com/articles/10.1186/s40900-016-0023-1

292. McCann SK, Campbell MK, Entwistle VA. Reasons for participating in randomised

controlled trials: conditional altruism and considerations for self. Trials [Internet]. 2010 Dec 22 [cited 2019 Mar 18];11(1):31. Available from: https://trialsjournal.biomedcentral.com/articles/10.1186/1745-6215-11-31

293. Kossoff EH, Zupec-Kania BA, Amark PE, Ballaban-Gil KR, Bergqvist CAG, Blackford R, et al. Optimal clinical management of children receiving the ketogenic diet: Recommendations of the International Ketogenic Diet Study Group. Epilepsia [Internet]. 2009 Jan 27 [cited 2017 Jul 14];50(2):304–17. Available from: http://www.ncbi.nlm.nih.gov/pubmed/18823325

294. National Institute for Health and Care Excellence [NICE]. Nutrition support for adults: oral nutrition support, enteral tube feeding and parenteral nutrition [clinical guideline 32]. 2006 [cited 2017 Jul 14]; Available from: https://www.nice.org.uk/guidance/cg32/chapter/1-Guidance#screening-for-malnutrition-and-the-risk-of-malnutrition-in-hospital-and-the-community

295. Sussman D, van Eede M, Wong MD, Adamson SL, Henkelman M. Effects of a ketogenic diet during pregnancy on embryonic growth in the mouse. BMC Pregnancy Childbirth [Internet]. 2013 May 8 [cited 2017 Jul 14];13:109. Available from: http://www.ncbi.nlm.nih.gov/pubmed/23656724

APPENDIX A: EXAMPLE SEARCH STRATEGY – MEDLINE (OVID)

1. (ketogenic or ketone or ketosis or carbohydrate restrict* or low carbohydrate or high fat or Atkin* or glyc*emic or triglyceride* or medium chain triglyceride*).af
2. (central nervous system or brain or cerebral or spinal or spine).af
3. (cancer or tumo*r or malignan* or neoplas* or carcinoma*).af
4. 2 and 3
5. (glioblastoma* or astrocytoma* or glioma* or ependymoma* or oligodendroglioma* or ganglioglioma* or medulloblastoma* or astrocytic* or ependymal*).af
6. 4 or 5
7. 1 and 6
8. Limit 7 to (English language and humans)

APPENDIX B: QUALITY APPRAISAL CHECKLIST FOR CASE SERIES STUIDES (129)

Quality Appraisal Checklist for Case Series Studies*

Assessor initials and date:			
Author(s) and date of publication:			
Study objective			
1.	**Was the hypothesis/aim/objective of the study clearly stated?**	Yes	☐
		Partial	☐
		No	☐
Study design			
2.	**Was the study conducted prospectively?**	Yes	☐
		Unclear	☐
		No	☐
3.	**Were the cases collected in more than one centre?**	Yes	☐
		Unclear	☐
		No	☐
4.	**Were patients recruited consecutively?**	Yes	☐
		Unclear	☐
		No	☐
Study population			
5.	**Were the characteristics of the patients included in the study described?** *(Number of patients, age, gender, disease, treatment history)*	Yes	☐
		Partial	☐
		No	☐
6.	**Were the eligibility criteria (i.e. inclusion and exclusion criteria) for entry into the study clearly stated?**	Yes	☐
		Partial	☐
		No	☐
7.	**Did patients enter the study at a similar point in the disease?** *(Stage of disease, prior treatment)*	Yes	☐
		Unclear	☐
		No	☐
Intervention and co-intervention			
8.	**Was the intervention of interest clearly described?** *(Diet, duration, administration)*	Yes	☐
		Partial	☐
		No	☐
9.	**Were additional interventions (co-interventions) clearly described?** *(Oncological treatments, holistic treatments, involvement in other trials, include details of type, dose, frequency/duration)*	Yes	☐
		Partial	☐
		No	☐

Outcome measure			
10.	**Were relevant outcome measures established a priori?**	Yes	☐
		Partial	☐
		No	☐
11.	**Were outcome assessors blinded to the intervention that patients received?**	Yes	☐
		Unclear	☐
		No	☐
12.	**Were the relevant outcomes measured using appropriate objective/subjective methods?** *Overall survival – time to death from specific time point* *Progression free survival – time to progression from specific time point* *Quality of life – questionnaire* *Acceptability – questionnaire* *Tolerance – quantification of gastrointestinal tolerance* *Compliance - ketosis* *Ketone levels – blood or urinary ketone monitoring* *Glucose levels – blood glucose monitoring*	Yes	☐
		Partial	☐
		No	☐
13.	**Were the relevant outcome measures made before and after the intervention?**	Yes	☐
		Unclear	☐
		No	☐
Statistical analysis			
14.	**Were the statistical tests used to assess the relevant outcomes appropriate?** *(If no tests used reasons why should be stated)*	Yes	☐
		Unclear	☐
		No	☐
Results and conclusions			
15.	**Was follow-up long enough for important events and outcomes to occur?** *(8 weeks short term follow up)*	Yes	☐
		Unclear	☐
		No	☐
16.	**Were losses to follow-up reported?**	Yes	☐
		Unclear	☐
		No	☐
17.	**Did the study provided estimates of random variability in the data analysis of relevant outcomes?** *(Standard deviations, confidence intervals, range, interquartile range reported or can be calculated from raw data)*	Yes	☐
		Partial	☐
		No	☐
18.	**Were the adverse events reported?**	Yes	☐
		Partial	☐
		No	☐
19.	**Were the conclusions of the study supported by results?**	Yes	☐
		Unclear	☐
		No	☐
Competing interests and sources of support			
20.	**Were both competing interests and sources of support for the study reported?**	Yes	☐
		Partial	☐
		No	☐

*Note: Assessor specific additions as advised by authors of tool highlighted in red.

APPENDIX C: CHARACTERISTICS OF INCLUDED STUDIES

Champ et al., (2014)	
Methods	Retrospective case series.
Population	6 patients aged 34-62 years, of unspecified gender, with a histological diagnosis of glioblastoma. Study undertaken in USA.
Intervention	KD containing less than 50g carbohydrate/day. Duration 3-12 months.
Outcomes	• Overall survival • Progression free survival • Adverse events • Retention rates • Tolerance • Ketone levels • Glucose levels
Notes	Previous treatment options varied from biopsy (n=1), to subtotal resection (n=2), to gross total resection (GTR) (n=2), to GTR with Glidel wafers (n=1). Medical intervention during diet varied from radiotherapy and temozolomide (n=4), temozolomide (n=1) and temozolomide and cediranib (n=1). Mean serum glucose levels of 53 controls (grade III and IV gliomas) were noted but not directly compared to the KD patients to assess statistical significance; therefore the assessors deemed the study to be a case series.
Risk of bias	
Study objectives (quality of reporting)	Clear aim.
Study design (study execution)	Retrospective study, with unclear centre allocations, but consecutive recruitment.
Study population (study execution)	Patient characteristics described with clear eligibility criteria. Patients entered the study at similar points in the disease.
Intervention and co-intervention (quality of reporting)	The dietary intervention and the co-medical interventions were clearly described.
Outcome measures (study execution)	Relevant outcome measures were partially stated priori, but all outcome measures were assessed using the appropriate methods. It is unclear if outcome assessors were blinded to the intervention. Unclear if all outcome measures were assessed pre and post intervention.
Statistical analysis (study execution)	Unclear statistical testing.
Results and conclusions (study execution and quality of reporting bias)	Adequate duration of follow up, including reported losses. Random variability of data was partially reported. Adverse events were fully reported and conclusions were supported by study results.
Competing interests and sources of support (quality of reporting)	No conflict of interest.

Nebeling et al., (1995)	
Methods	Prospective case series.
Population	2 female patients. One aged 3 years with grade IV anaplastric astrocytoma of the spinal cord and one aged 8.5 years with grade III cerebellar astrocytoma. Study undertaken in USA.
Intervention	Medium chain triglyceride KD (60% MCT, 10% carbohydrate, 20% protein), provided to 120% recommended daily allowance. Gastrostomy fed (n=1). Duration 2-14 months (protocol 2 months).
Outcomes	• Overall survival • Progression free survival • Adverse events • Retention rates • Dietary compliance
Notes	Previous treatment options varied from radiotherapy (3600cGys) and chemotherapy (n=1) to multiple surgeries, shunt, radiotherapy (5400 cGys) and chemotherapy (n=1). Medical intervention during diet consisted of chemotherapy (n=1) or no treatment (n=1). Dietary tolerance and quality of life were commented upon, however lacked objective/subjective methods of measurement.
Risk of bias	
Study objectives (quality of reporting)	Clear aim.
Study design (study execution)	Prospective, single centre, case series. Unclear if recruitment was consecutive.
Study population (study execution)	Patient characteristics described, no eligibility criteria identified, with patients entering the study at different points of disease.
Intervention and co-intervention (quality of reporting)	The dietary intervention and the co-medical interventions were clearly described.
Outcome measures (study execution)	Relevant outcome measures were stated priori and partially measured using the appropriate objective/subjective measures. It is unclear if outcome assessors were blinded to the intervention. Unclear if all outcome measures were assessed pre and post intervention.
Statistical analysis (study execution)	No statistical tests undertaken.
Results and conclusions (study execution and quality of reporting bias)	Adequate duration of follow up, including reported losses. Random variability of data was not reported. Adverse events were fully reported and conclusions were supported by study results.
Competing interests and sources of support (quality of reporting)	Sources of support declared.

Rieger et al., (2014)	
Methods	Prospective case series.
Population	20 patients (n=13 females), aged 30 to 72 years (median 57 years), with recurrent glioblastoma. Study undertaken in Germany.
Intervention	KD containing 60g carbohydrate per day, with the addition of fermented yoghurt drinks (500ml per day) and two plant oils (basic oil and additional oil). Duration 6-42 months.
Outcomes	• Overall survival • Progression free survival • Adverse events • Retention rates • Dietary compliance • Dietary tolerance • Quality of life • Ketone levels • Glucose levels
Notes	Previous treatment options varied from radiotherapy (n=20), concomitant temozolomide (n=16), temozolomide 5/28 (n=18), temozolomide 7/14 (n=18), nitrosourea-based chemotherapy (n=5), carmustine wafer (n=1) and bevacizumab + lomustine (n=1). Medical intervention during diet varied from teniposide (n=1), bevacizumab (n=4), bevacizumab and irinotecan (n=3), no treatment (n=13). Details of plant oils unidentifiable.
Risk of bias	
Study objectives (quality of reporting)	Clear aim and outcomes.
Study design (study execution)	Prospective, single centre pilot study with consecutive recruitment. Protocol utilised. Registration number NCT0057146.
Study population (study execution)	Patient characteristics described with clear eligibility criteria. Patients entered the study at similar points in the disease.
Intervention and co-intervention (quality of reporting)	The dietary intervention and the co-medical interventions were clearly described.
Outcome measures (study execution)	Relevant outcome measures were stated priori and partially measured using the appropriate objective/subjective measures. It is unclear if outcome assessors were blinded to the intervention. Unclear if all outcome measures were assessed pre and post intervention.
Statistical analysis (study execution)	Appropriate statistical testing.
Results and conclusions (study execution and quality of reporting bias)	Adequate duration of follow up, including reported losses. Random variability of data and adverse events were fully reported. Conclusions were supported by study results.
Competing interests and sources of support (quality of reporting)	Competing interests and sources of support reported.

Schwartz et al., (2015)	
Methods	Prospective case series.
Population	2 male patients aged 52 and 55 years, with glioblastoma. Study undertaken in USA.
Intervention	Energy restricted 3:1 KD (3g fat to 1g of carbohydrate and protein combined) consumed orally through a commercially available formula (Ketocal®; Nutricia North America). Proceeded by 48hour fast. Duration 1-3 months (protocol 3 months).
Outcomes	• Progression free survival • Adverse events • Retention rates • Dietary compliance • Ketone levels • Glucose levels
Notes	Previous treatment options were consistent in both patients; surgery, radiotherapy and temozolomide. Medical intervention during diet not stated. 1 patient switched from commercial formula to food of the same KD ratio at day 6 due to palatability.
Risk of bias	
Study objectives (quality of reporting)	Aim not clearly stated.
Study design (study execution)	Retrospective study, with unclear centre allocations and unclear if consecutively recruited.
Study population (study execution)	Patient characteristics described with clear eligibility criteria. Patients entered the study at similar points in the disease.
Intervention and co-intervention (quality of reporting)	The dietary intervention and the co-medical interventions were clearly described.
Outcome measures (study execution)	Relevant outcome measures were partially stated priori, but all outcome measures were assessed using the appropriate methods. It is unclear if outcome assessors were blinded to the intervention. Relevant outcome measures were assessed pre and post intervention.
Statistical analysis (study execution)	Unclear statistical testing.
Results and conclusions (study execution and quality of reporting bias)	Adequate duration of follow up, including reported losses. Random variability of data was not reported. Adverse events were fully reported and conclusions were supported by study results.
Competing interests and sources of support (quality of reporting)	No conflict of interest.

Strowd et al., (2015)	
Methods	Retrospective case series.
Population	8 patients (n=6 males), aged 28 to 54 years, with glioma (n=3 low grade oligodendroglioma, n=1 low grde astrocytoma, n=1 anaplastic astrocytoma, n=3 glioblastoma) and resultant seizure disorders. Study undertaken in USA.
Intervention	Modified Atkins diet (MAD) 15g carbohydrate per day (n=1) to 20g carbohydrate per day (n=7). Duration 2-24 months.
Outcomes	• Overall survival • Adverse events • Retention rates
Notes	Previous treatment options varied from surgery (n=2), surgery, radiotherapy and temozolomide (n=4), surgery and temozolomide (n=1) and surgery, radiotherapy, temozolomide, bevacizumab, ICT- 107 and veliparib (n=1). Medical intervention during diet varied from temozolomide (n=1), bevacizumab and LBH589 (n=1), temozolomide and bevacizumab (n=1) and no treatment (n=5).
Risk of bias	
Study objectives (quality of reporting)	Clear aim.
Study design (study execution)	Retrospective single centre study, unclear if consecutively recruited.
Study population (study execution)	Patient characteristics described, with partially identified eligibility criteria. Patients entered the study at different points of disease.
Intervention and co-intervention (quality of reporting)	The dietary intervention and the co-medical interventions were clearly described.
Outcome measures (study execution)	Relevant outcome measures were not stated priori and unable to assess if outcome measures were assessed using the appropriate methods. It is unclear if outcome assessors were blinded to the intervention. Unclear if all outcome measures were assessed pre and post intervention.
Statistical analysis (study execution)	Appropriate statistical testing.
Results and conclusions (study execution and quality of reporting bias)	Adequate duration of follow up, including reported losses. Random variability of data and adverse events were fully reported. Conclusions were supported by study results.
Competing interests and sources of support (quality of reporting)	Competing interests and sources of support reported.

Zuccoli et al., (2010)	
Methods	Retrospective case series.
Population	1 female patient, aged 65 years with glioblastoma. Study undertaken in Italy.
Intervention	Energy restricted 1:1 KD (600kcals/day, 10g carbohydrate, 32g protein, 10g MCT oil, 20g 4:1 commercially available formula [Ketocal®; SHS International] and total fat content of 42g). Proceeded by 72 hour fast. Duration 1.8 months (56 days).
Outcomes	• Progression free survival • Adverse events • Ketone levels • Glucose levels
Notes	ERKD proceeded and concluded with a low calorie diet (600kcals/day). Previous treatment option included incomplete debulking (MGMT positive). Medical intervention during diet included radiotherapy and temozolomide.
Risk of bias	
Study objectives (quality of reporting)	Aim not clearly stated.
Study design (study execution)	Retrospective single centre study, recruiting 1 patient.
Study population (study execution)	Patient characteristics described, with no eligibility criteria.
Intervention and co-intervention (quality of reporting)	The dietary intervention and the co-medical interventions were clearly described.
Outcome measures (study execution)	Relevant outcome measures were not stated priori and partially measured using the appropriate objective/subjective measures. It is unclear if outcome assessors were blinded to the intervention. Unclear if all outcome measures were assessed pre and post intervention.
Statistical analysis (study execution)	No statistical testing undertaken.
Results and conclusions (study execution and quality of reporting bias)	Adequate duration of follow up, including reported losses. Random variability of data was not reported. Adverse events were fully reported and conclusions were supported by study results.
Competing interests and sources of support (quality of reporting)	No conflict of interest.

APPENDIX D: CHARACTERISTICS OF ONGOING TRIALS

Ghodsi, (2012)	
Trial name or title	Therapeutic effect of KD on survival and quality of patients with glioblastoma multiforme
Study identifier	IRCT201204099417N1
Methods	Single centre, single group, open label trial.
Population	Aimed to recruit 20 participants with glioblastoma. Included participants will be aged > 49 years, Karnovsky Performance Score >69, surgical intervention and histological confirmation of glioblastoma, undergone chemotherapy and radiotherapy. Potential participants will be excluded if other diagnoses are suspected, cannot tolerate KD, KD is contraindicated, participant does not agree to regime protocol. Study undertaken in Iran.
Interventions	Energy restricted MCT KD (50% MCT, energy restricted to 25kcal/kg/day).
Outcomes	Primary outcomes: • Survival (defined as time until death). Secondary outcomes: • Quality of life (assessed by 'FIM form').
Starting date	May 2010.
Contact information	ghodsism@tums.ac.ir
Notes	Unable to locate definition of FIM form as quality of life measure. Expected completion unknown.

Guimaraes Santos & Perieia da Fonseca, (2016)	
Trial name or title	Ketogenic diet combined with intranasal administration of perillyl alcohol: strategy therapy to refractory Glioblastoma Multiforme to standard treatment
Study identifier	RBR-8x8fd9
Methods	Single centre, parallel group, open label trial.
Population	Aimed to recruit 30 participants with recurrent glioblastoma inhaling perillyl alcohol. Included participants will have recurrent glioblastoma, aged 20 to 65 years, received standard therapy (chemotherapy ± radiotherapy), inhaling perillyl alcohol. Potential participants will be excluded if experience neurological complications, terminal phase or discontinue diet. Study undertaken in Brazil.
Interventions	KD v control, both groups inhaling perillyl alcohol.
Outcomes	Primary outcomes: • Comparison of tumour growth by anterior cerebral magnetic resonance imaging at baseline and after 3 months of combined therapy with inhalation of perillil alcohol and ketogenic diet. Secondary outcomes: • Anthropometric changes before and after dietary intervention.
Starting date	October 2015.
Contact information	julianaguima86@gmail.com
Notes	Expected completion not stated.

Jameson, (2014)	
Trial name or title	Pilot study evaluating progression free survival in patients using KD while receiving chemoradiation for glioblastoma multiforme
Study identifier	ACTRN12614001056684.
Methods	Single centre, single group, open label phase II pilot study.
Population	Aimed to recruit 20 participants with glioblastoma suitable for standard chemoradiotherapy. Included participants will have histologically confirmed glioblastoma, suitable for standard chemoradiotherapy, mentally competent to understand the requirements of the diet and believe that they are able of achieving them, able to give written informed consent. No age limitations applied. Potential participants will be excluded if diagnosed with diabetes mellitus and are at risk of hypoglycaemic episodes, currently pregnant or breastfeeding. Study undertaken in New Zealand.
Interventions	KD (<30g carbohydrate/day).
Outcomes	Primary outcomes: • Progression free survival. Secondary outcomes: • Achievement of ketosis on urinary ketone testing. • Compliance with chemoradiotherapy (assessed through treatment charts). • Compliance with KD (assessed by dietitian from 3 day food diaries and 24 hour food intake recall). • Food satisfaction (assessed through visual analogue scale). • Patient generated subjective global assessment (of malnutrition, nutritional intake and appetite). • Proportion of patients with adverse events related to KD.
Starting date	October 2014.
Contact information	michael.jameson@waikatodhb.health.nz
Notes	Expected completion not stated.

Klein, (2014)	
Trial name or title	Ketogenic diet treatment adjuvant to radiation and chemotherapy in glioblastoma multiforme: a pilot study (GBMXRT)
Study identifier	NCT02302235.
Methods	Single centre, parallel group, randomised control, open label, phase II pilot study.
Population	Aimed to recruit 6 participants with newly diagnosed glioblastoma. Included participants will be aged 18-65 years, able and willing to sign a consent form, histologically confirmed glioblastoma, documented surgical resection or debulking, measurable contrast enhancing progressive or recurrent glioblastoma, by MRI imaging ≤2 weeks before screening or prior to surgery if done ≤2 months before, Karnovsky Performance Score of 70 or more. Potential participants will be excluded if experienced acute intracranial intratumoural haemorrhage, prior treatment with small-molecule kinase inhibitor, non-cytotoxic hormonal agent, KD ≤6 months of enrolment, planned continued use of glucocorticoids, any systemic illness or unstable medical condition that may pose additional risk (e.g. cardiac, endocrine disturbances, renal or liver disease), history of non-glioma malignancy other than surgically excised non-melanoma skin cancer or in situ carcinoma of the cervix, history of uncontrolled hyperlipidaemia, active drug or alcohol dependence, human immunodeficiency virus, hepatitis C, failure to recover from grade 2 toxicities, pregnancy, breastfeeding, use of an investigational drug within 1 month of enrolment, inability or unwillingness to give written informed consent. Study undertaken in the USA.
Interventions	Energy restricted 4:1 KD (1600kcals/day), commenced at initiation of radiotherapy treatment compared to standard diet at initiation of radiotherapy treatment, randomised at a ratio of 1:1.
Outcomes	Primary outcomes: • Survival time. • Time to radiological (MRI) tumour progression (defined by radiographic assessment in neuro-oncology criteria based on contrast-enhanced cranial MRI scans evaluating measureable disease, measured as the sum of products of perpendicular diameters (bi-dimensional measurements) of all measurable enhancing lesions and non-measurable disease). • Incidence of treatment emergent adverse events (defined as Incidence of treatment-emergent adverse events changes in laboratory evaluations, changes in physical examination findings will be compared between the KD and control treatment groups). Secondary outcomes: • Tolerability of KD (defined as unwillingness by the subject to continue with the diet because of possible diet related side effects).
Starting date	February 2014.
Contact information	kleinp@epilepsydc.com
Notes	Expected completion August 2017.

Klein, (2016)	
Trial name or title	Ketogenic diet as adjuvant treatment in refractory/ end stage glioblastoma multiforme: a pilot study (KGDinGBM)
Study identifier	NCT01865162.
Methods	Single centre, single group, open label, phase I pilot study.
Population	Aimed to recruit 6 participants with treatment refractory glioblastoma. Included participants will be aged 18-65 years, able and willing to sign a consent form, histologically confirmed glioblastoma, documented recurrence or progression after surgical, radiotherapy and chemotherapy interventions, measurable contrast enhancing progressive or recurrent glioblastoma, by MRI imaging ≤2 weeks before screening, (a) ≥ 3months after completion of radiation; (b) 6 weeks from a nitrosourea chemotherapy; (c) ≥ weeks from a non-nitrosourea chemotherapy (all [a-c] in order to allow recovery from the potential of severe toxicity related to these treatments), Karnovsky Performance Score of 70 or more. Potential participants will be excluded if experienced acute intracranial intratumoural haemorrhage, prior treatment with small-molecule kinase inhibitor, non-cytotoxic hormonal agent, KD ≤6 months of enrolment, planned continued use of glucocorticoids, any systemic illness or unstable medical condition that may pose additional risk (e.g. cardiac, endocrine disturbances, renal or liver disease), history of non-glioma malignancy other than surgically excised non-melanoma skin cancer or in situ carcinoma of the cervix, history of uncontrolled hyperlipidaemia, active drug or alcohol dependence, human immunodeficiency virus, hepatitis C, failure to recover from grade 2 toxicities, pregnancy, breastfeeding, use of an investigational drug within 1 month of enrolment, inability or unwillingness to give written informed consent. Study undertaken in the USA.
Interventions	Energy restricted 4:1 KD (1600kcals/day), followed until exit criteria are met or for 6 months (exit criteria consists of death or use of glucocorticoids).
Outcomes	Primary outcomes: • To evaluate the safety of KD (defined as early treatment discontinuation, treatment compliance, 7-point Licker hunger scale, fasting lipid levels, fasting serum glucose and insulin levels). Secondary outcomes: • To obtain pilot data on efficacy of KD (defined as survival time, time to cerebral oedema requiring steroid rescue treatment). • To evaluate tolerability of KD (defined as incidence of treatment-emergent adverse events during treatment).
Starting date	January 2013.
Contact information	kleinp@epilepsydc.com
Notes	Expected primary completion May 2017.

Rieger & Steinbach, (2012)	
Trial name or title	Calorie-restricted, ketogenic diet and transient fasting during reirradiation for patients with recurrent glioblastoma (ERGO2)
Study identifier	NCT01754350.
Methods	Single centre, parallel group, randomised control, open label, trial.
Population	Aimed to recruit 50 participants requiring reirradiation for recurrent glioblastoma. Included participants will be aged 18 years and over, recurrence of histologically confirmed glioblastoma, at least 6 months after first surgery, at least 6 months after first radiotherapy, interdisciplinary recommendation for reirradiation, Karnovsky Performance Score ≥ 60, creatinine ≤2mg/dl, urea ≤100mg/dl, ALAT/ALST ≤7 times the upper limit. Potential participants will be excluded if bowel obstruction/ ileus, insulin dependent diabetes, decompensated heart failure, myocardial infarction within last 6 months, symptomatic arterial fibrillation, severe acute infection, malnutrition, cachexia, other medical conditions that might increase the risk of dietary intervention, pregnancy, uncontrolled thyroid function, pancreatic insufficiency, dementia or clinically relevant alterations of the mental state which could impair the ability to implement the diet or given informed consent. Study undertaken in Germany.
Interventions	Energy restricted KD with transient fasting (day 1-3 and day 7-9, restriction of carbohydrates to < 60 g and of energy to 21-23 kcal/kg per day, day 4-6 fasting) compared to standard nutrition (nutrition as recommended by the German Society for Nutrition, energy to 30 kcal/kg per day).
Outcomes	Primary outcomes: • Progression free survival (defined as progression free survival rates 6 months after reirradiation). Secondary outcomes: • Feasibility (measured as median number on diet per patient and average energy and carbohydrate intake per day during day 1-9). • Safety and tolerability (defined as number of patients with adverse events). • Progression free survival (defined as progression free survival rates 1 and 3 months after reirradiation). • Overall survival after reirradiation. • Frequency of seizures (during days 1-12). • Ketosis (urine and blood ketones and metabolic parameters [glucose, insulin, IGF-1] during days 1-12). • Quality of life (measured by EORTC quality of life questionnaire at days 1-12). • Depression (measured by SCL-90 at days 1-12). • Attention (measured by d2-testing at days 1-12). • Response (response assessment 1 month after reirradiation).
Starting date	May 2013.
Contact information	johannes.rieger@med.uni-frankfurt.de
Notes	Expected completion October 2017.

Scheck, (2014)	
Trial name or title	Ketogenic diet with radiation and chemotherapy for newly diagnosed glioblastoma.
Study identifier	NCT02046187.
Methods	Single centre, single group, open label, phase I/II prospective trial.
Population	Aimed to recruit 14 participants with newly diagnosed glioblastoma. Included participants will be aged 18-80 years, histological confirmation of glioblastoma, Zubrod Performance Score of <2, able to undergo MRI imaging with gadolinium, access to a computer and internet. Potential participants will be excluded if unable to undergo MRI with gadolinium, genetic disorders of fat metabolism, receiving sodium valproate, diabetes, enrolled into other glioblastoma trial. Study undertaken in USA.
Interventions	4:1 KD commenced prior to initiation of radiotherapy and chemotherapy, followed by modified Atkins diet during monthly chemotherapy.
Outcomes	Primary outcomes: • Number of participants with adverse events (defined as adverse events from initiation of diet until end of radiation). Secondary outcomes: • Overall survival. • Time to progression. • Quality of life.
Starting date	October 2013.
Contact information	Not provided.
Notes	Expected completion March 2017. Study ongoing, but not recruiting participants.

Schwartz, (2012)	
Trial name or title	Pilot study of a metabolic nutritional therapy for the management of primary brain tumours (KETONES)
Study identifier	NCT01535911.
Methods	Single centre, single group, open label, pilot study.
Population	Aimed to recruit 12 participants with newly diagnosed glioblastoma. Included participants will be 18 to 90 years, histologically proven glioblastoma, measurable disease after standard therapies, Eastern Cancer Oncology Group performance status of ≤2, life expectancy >3 months. Potential participants will be excluded if diagnosed with diabetes mellitus requiring medication, concomitant use of glucocorticoids, cholecystectomy within 1 year prior to study, inability to adhere to or tolerate dietary protocol, active malignancy other than primary brain tumour, participation in investigational study 2 weeks prior to study entry, pregnancy, inability to give informed consent. Study undertaken in USA.
Interventions	Energy restricted KD (20-25kcals/kg/day).
Outcomes	Primary outcomes: • Changes in brain tumour size (assessed by comparing MRI images obtained at beginning of study with those after completion of radiotherapy and after an additional 6 weeks of diet).
Starting date	April 2012
Contact information	ken.schwartz@hc.msu.edu
Notes	Expected completion July 2017.

Song, (2016)	
Trial name or title	Ketogenic diet adjunctive to salvage chemotherapy for recurrent glioblastoma: a pilot study (KGDinrGBM)
Study identifier	NCT02939378.
Methods	Single centre, parallel group non-randomised control, open label, phase II pilot study.
Population	Aimed to recruit 60 participants with recurrent glioblastoma. Included participants will be aged 18-60 years, Karnovsky Performance Score of 60 or more, histologically confirmed glioblastoma grade IV, ability and willingness to sign consent form, documented recurrence or progression after surgical resection/ debulking, radiation and temozolomide chemotherapy, normal function of liver and kidney. Potential participants will be excluded if any systemic illness or unstable medical condition that may pose additional risk (e.g. cardiac, endocrine disturbances, renal or liver disease), history of uncontrolled hyperlipidaemia or hyperglycaemia, human immunodeficiency virus, hepatitis C, pregnancy, breastfeeding, inability or unwillingness to give written informed consent. Study undertaken in China.
Interventions	KD compared to standard diet.
Outcomes	Primary outcomes: • Number of participants with treatment emergent adverse effects (defined as number of participants with treatment emergent adverse effects while on KD). Secondary outcomes: • Chemo sensitivity of tumour (defined as MRI measured changes in tumour size). • Overall survival (defined as time to reported death). • Ketosis (defined as urinary and blood ketone measurements). • Quality of life (defined by Karnovsky Performance Score).
Starting date	October 2016.
Contact information	linsong2005@126.com
Notes	Unclear methods for recruitment to and comparison of arms. Type of KD not defined. Expected completion December 2018.

Strowd, (2014)	
Trial name or title	Glioma modified Atkins based diet in patients with glioblastoma (GLAD)
Study identifier	NCT02286167.
Methods	Multi centre, single group, open label feasibility study.
Population	Aimed to recruit 25 participants with glioblastoma. Included participants will be aged 18 years or over, histological confirmation of glioblastoma, completed >80% concurrent radiation therapy and adjuvant temozolomide without CTCAE grade 3 or 4 toxicities, be greater than 7 months from time of completing concurrent chemoradiotherapy, Karnovsky Performance Score ≥60, appropriate mental capacities with sufficient social support to be able to complete study activities and able to provide written consent. Potential participants will be excluded if have a history of metabolic disorders, server acute infection, BMI >35 or <20 kg/m^2, active bowel obstruction or ileus, active or remote pancreatitis, clinically significant hear failure, recent myocardial infarction, symptomatic atrial fibrillation, significant renal disease, significant hepatic dysfunction, insulin dependent diabetes mellitus, conditions that may increase the risk of the diet or significantly reduce compliance, concurrent experimental therapies, milk allergy, prior treatment with MAD within 9 months prior to study enrolment, inability to complete 3 day baseline screening diet record. Study undertaken in USA.
Interventions	MAD with intermittent fasting.
Outcomes	Primary outcome: • Feasibility of intermittent MAD in patients with glioblastoma (defined as the number of patients able to maintain the diet and achieve nutritional goals). Secondary outcomes: • Biological activity (measured by pre and post study cerebral glutamate and glutamine concentrations by MRS). • Tolerability (defined by percentage of patients who have an adverse reaction of any grade attributed to the diet). • Dietary activity (compliance assed by serial changes in serum glucose, ketones, weight, body fat composition, change in seizure frequency without anti-epileptic drug adjustment).
Starting date	November 2014.
Contact information	rstrowd@wakehealth.edu
Notes	Details of fasting regime not disclosed. Expected completion November 2018.

Vaisman, (2010)	
Trial name or title	The effect of ketogenic diet on malignant tumours – recurrence and progress
Study identifier	NCT01092247.
Methods	Single centre, parallel group, open label trial.
Population	Aimed to recruit 40 participants with recurrent or progressive high grade glioma. Included participants will be aged 18 years or over, recurrent or progressive high grade glioma after failure of at least one standard oncological treatment, gliomatosis cerebri including patients declining radiation treatment. Potential participants will be excluded if have malignant tumours and are receiving treatment at time of recruitment, early termination (patients who discontinue the KD and return to standard diet). Study undertaken in Israel.
Interventions	KD compared to standard diet.
Outcomes	Primary outcome: • To study the effect of KD on tumour growth progression and longevity in patients with malignant glioblastoma (defined as tumour size in repeated MRI studies). Secondary outcomes: • Performance scale (defined by Karnovsky Performance Score). • Quality of life (defined by EQ5D scale).
Starting date	March 2010.
Contact information	vaisman@tasmc.health.gov.il
Notes	Type of KD not defined. Expected completion May 2011 (last updated March 2010).

APPENDIX E: WCFT SURVEY EXPLORING KD FOR PATIENTS WITH GLIOMAS

The Walton Centre NHS
NHS Foundation Trust
Excellence in Neuroscience

Dietary Treatment for Brain Gliomas

Gliomas

Since the early 1920's a great deal of research has looked at how altering the type of energy that the body uses can affect the severity and progression of certain diseases. The 'Ketogenic Diet' (KD) encourages the body to produce and use ketones as its primary energy instead of glucose and has been successful in the treatment of childhood epilepsy. More recently, KD has been considered for use in patients with gliomas as these tumours use glucose, not ketones, as their main energy source. By limiting the tumour's main energy source, it may be possible to prevent tumour growth and even promote shrinkage. Further, this switch from glucose to ketones may make the tumours more responsive to radiotherapy and chemotherapy. A small number of case reports have suggested beneficial effects of the KD on tumour progression; however well-controlled clinical trials are needed.

The Ketogenic Diet

Commitment to the KD involves many lifestyle alterations which can be challenging. For these reasons, a number of variations of the KD exist which have been shown to have positive results. This survey will focus on a less restrictive form of the diet known as the Modified Atkins Diet (MAD).

The MAD is based on the weight loss diet first described by Dr Robert C. Atkins in 1972. It restricts carbohydrates to around 10-20 grams per day (an example of this being 10 strawberries, 20 raspberries, 2 beetroot and 2 carrots over the course of a day) and encourages a high intake of fat which will provide around 65% of total dietary energy. Compared to the stricter forms of the KD, the MAD doesn't limit or strictly measure proteins or calories but does require close monitoring under the supervision of a registered dietitian.

Monitoring is important as some people who follow the MAD may experience some side effects due to restricting carbohydrates and increasing their intake of fats. These side effects may include:

- Altered or raised cholesterol or blood lipids
- Constipation
- Acid reflux
- Kidney stones
- Decreased bone density

The likelihood of experiencing these side effects varies from person to person, where some people may not experience any, whilst others may experience one or more at once. Those following the diet must be monitored by a dietitian so that any side effects can be recognised and treated as soon as possible.

Survey

Currently, the KD is not routinely available for patients with gliomas in the NHS as:

a) We do not know whether the diet is acceptable to adults
b) We do not know whether patients would want to follow it in the longer term
c) We do not know whether patients would want access to the treatment
d) Most hospitals do not have dietitians who are funded to support the treatment

We would like you to complete this survey to help us decide whether patients with gliomas attending the Walton Centre clinics would like access to the KD. Following this, we will then be in a position to assess whether it would be feasible to run a clinical study in the future.

For each of the questions below, please enter a tick in the appropriate box:

Section 1		
1.	**Please select your age category:**	**Tick**
	a) 16-29 years	
	b) 30-49 years	
	c) 50-69 years	
	d) 70+ years	
2.	**Please select your gender:**	
	a) Male	
	b) Female	
	c) Don't wish to disclose	
4.	**Please write your postcode below:**	

Section 2			
1.	**Do you do your main weekly food shop at these stores:**	**Yes**	**No**
	a. Tesco?		
	b. Sainsbury's?		
	c. Asda?		
	d. Aldi?		
	e. Morrisons?		
	f. Other? please write here:		
2.	**Do you follow a vegan diet?**		
3.	**Do you have any difficulty preparing or cooking meals?**		
4.	**Do you use ready meals (e.g. microwave meals)?**		
5.	**If 'yes' how frequently do you use ready meals?**		**Tick**
	a) Daily		
	b) Weekly		
	c) Fortnightly		
	d) Monthly		

Section 3				
		Yes	**No**	**Unsure**
1.	**Should patients with gliomas have access to the ketogenic diet?**			
2.	**Would you like access to the ketogenic diet?**			

3.	**Would you be willing to try the diet for a few months to find out if it works for you?**			
4.	**Thinking about your treatment to date, when would you have considered starting this diet?**		**Tick**	
	Before surgery? (i.e. within a week of seeing your neurosurgeon)			
	After surgery? (i.e. within 2 weeks to 3 months of discharge from hospital)			
	After surgery but before radiotherapy?			
	After radiotherapy whilst receiving chemotherapy?			
		Yes	**No**	**Unsure**
5.	**Would you be interested in taking part in a clinical study to try and work out whether the diet can be delivered and is tolerable?**			
6.	**If 'yes', would you still be interested in taking part in a study if half the people were given the diet and the other half had standard treatment as usual?**			
7.	**What would be your motivators to participating in the study? (tick all the apply)**		**Tick**	
	a) To help other adults with glioma			
	b) To access the diet myself			
	c) To get expert advice about the diet			
	d) To improve quality of life			
	e) Other (please state):			
8.	**What would be your barriers to participating in the study? (tick all that apply)**			
	a) Extra burden of visiting a dietitian			
	b) Not enough time to devote to the study			
	c) Extra expense of travelling			
	d) Extra expense of the diet			
	e) Don't want to be involved in the study			
	f) Other (please state):			

Please write any additional comments below:

If you would like to be considered to take part in a clinical study in the future please send an email with your name and contact details to KD.glioma@thewaltoncentre.nhs.uk

APPENDIX F: NATIONAL SURVEY EXPLORING KD FOR PATIENTS WITH GLIOMAS

The Walton Centre NHS
NHS Foundation Trust
Excellence in Neuroscience

Dietary Treatment for Brain Gliomas

Gliomas

Since the early 1920's a great deal of research has looked at how altering the type of energy that the body uses can affect the severity and progression of certain diseases. The 'Ketogenic Diet' (KD) encourages the body to produce and use ketones as its primary energy instead of glucose and has been successful in the treatment of childhood epilepsy. More recently, KD has been considered for use in patients with gliomas as these tumours use glucose, not ketones, as their main energy source. By limiting the tumour's main energy source, it may be possible to make the tumours more responsive to radiotherapy and chemotherapy, slowing tumour growth. A small number of case reports have suggested beneficial effects of the KD on tumour progression; however well-controlled clinical trials are needed.

The Ketogenic Diet

Commitment to the KD involves many lifestyle alterations which can be challenging. For these reasons, a number of variations of the KD exist which have been shown to have positive results. This survey will focus on a less restrictive form of the diet known as the Modified Atkins Diet (MAD).

The MAD is based on the weight loss diet first described by Dr Robert C. Atkins in 1972. It restricts carbohydrates to around 10-20 grams per day (an example of this being 10 strawberries, 20 raspberries, 2 beetroot and 2 carrots over the course of a day) and encourages a high intake of fat which will provide around 65% of total dietary energy (from including foods like double cream, oil, butter and mayonnaise in meals). Compared to the stricter forms of the KD, the MAD doesn't limit or strictly measure protein (such as red meat, chicken and fish) or calories but does require close monitoring under the supervision of a registered dietitian. For example, the dietitian may monitor your weight, bloods and ketone levels then make changes to the diet if required.

Monitoring is important as some people who follow the MAD may experience some side effects due to restricting carbohydrates and increasing their intake of fats. These side effects may include:

- Altered or raised cholesterol or blood lipids
- Constipation
- Acid indigestion
- Kidney stones
- Decreased bone density

The likelihood of experiencing these side effects varies from person to person, where some people may not experience any, whilst others may experience one or more at once. Those

following the diet must be monitored by a dietitian so that any side effects can be recognised and treated as soon as possible. Due to these side effects the KD is not suitable for everyone.

Currently, the KD is not routinely available for patients with gliomas in the NHS as:

e) We do not know whether the diet is acceptable to adults
f) We do not know whether patients would want access to the diet
g) Most hospitals do not have dietitians who are funded to support the diet
h) Lack of robust clinical research in the area

Survey

We would like you to complete this survey to help us decide whether patients with gliomas would like access to the diet. Following this, we will then be in a position to assess whether it would be feasible to run a clinical study in the future.

For each of the questions below, please enter a tick in the appropriate box:

Section 1		
1.	**What type of glioma do you have?**	**Tick**
	d) Glioblastoma (grade IV)	
	e) Anaplastic astrocytoma or oligodendroglioma (grade III)	
	f) Low grade glioma (grade II astrocytoma or oligodendroglioma)	
	g) Other (please state)	
2.	**Have you received treatment (e.g. surgery, radiotherapy or chemotherapy) for a glioma?**	
	a) Yes	
	b) No	
3.	**Please select your age category:**	
	a) 16-29 years	
	b) 30-49 years	
	c) 50-69 years	
	d) 70+ years	
4.	**Please select your gender:**	
	a) Male	
	b) Female	
	c) Don't wish to disclose	

Section 2				
		Yes	**No**	**Unsure**
1.	**Since your diagnosis have you made any changes to your diet?**			
2.	**If 'yes' please state what changes you have made:**			
		Yes	**No**	**Unsure**

3.	**Did you know about the ketogenic diet prior to completing this survey?**			
4.	**If 'yes' where did you hear about the ketogenic diet?**			**Tick**
	a) Charity website			
	b) Clinical trials website			
	c) Online forum/blogs			
	d) Medical team			
	e) Patient support group			
	f) Other (please state):			
		Yes	**No**	**Unsure**
5.	**Should patients with gliomas have access to the ketogenic diet via the NHS?**			
6.	**Would you personally like access to the ketogenic diet?**			
7.	**Would you be willing to try the diet for 2-3 months to find out if it works for you?**			
8.	**Thinking about your treatment to date, when would you have considered starting this diet?**	**Yes**	**No**	**N/A**
	a) Before surgery? (i.e. within a week of seeing your neurosurgeon)			
	b) After surgery? (i.e. within 2 weeks to 3 months of discharge from hospital)			
	c) After surgery but before radiotherapy?			
	d) After radiotherapy whilst receiving chemotherapy?			
	e) After treatment and during monitoring phase?			
		Yes	**No**	**Unsure**
9.	**Would you be interested in taking part in a clinical study to try and work out whether the diet is effective and tolerable?**			
10.	**If 'yes', would you still be interested in taking part in a study if half the people were given the diet and the other half had standard treatment as usual?**			
11.	**What would be your motivators to participating in the study? (tick all the apply)**			**Tick**
	f) To help other adults with glioma			
	g) To access the diet myself			
	h) To get expert advice about the diet			
	i) To improve quality of life			
	j) Other (please state):			
12.	**What would be your barriers to participating in the study? (tick all that apply)**			
	g) Extra burden of visiting a dietitian			
	h) Not enough time to devote to the study			
	i) Extra expense of travelling			
	j) Extra expense of the diet			
	k) Don't want to be involved in the study			
	l) Fear of side effects			
	m) Carer or family burden			
	n) Other (please state):			

Please write any additional comments below:

APPENDIX G: EXIT SURVEY FOR THE KETOGENIC DIET SCOPING SERVICE FOR PATIENTS WITH GLIOMAS

The Walton Centre NHS
NHS Foundation Trust
Excellence in Neuroscience

Ketogenic Diet and Brain Glioma: Exit Survey

We are interested in hearing about your experience of the ketogenic diet at The Walton Centre. Following this we will then be in a position to assess whether it would be feasible to run a clinical study in the future and whether the diet could be offered to other adults with brain gliomas.

For each of the questions below, please enter a tick in the appropriate box/boxes:

Section 1		
1.	**Please select your age category:**	**Tick**
	e) 18-29 years	
	f) 30-49 years	
	g) 50-69 years	
	h) 70+ years	
2.	**Please select your gender:**	
	h) Male	
	i) Female	
	j) Don't wish to disclose	

Section 2		
1.	**How long have you followed a ketogenic diet for?**	**Tick**
	a) Less than 1 week	
	b) 1 week to 3 weeks	
	c) 4 weeks to 7 weeks	
	d) 8 weeks to 11 weeks	
	e) 12 weeks	
	f) More than 12 weeks (please state number of weeks ……..)	
2.	**Why did you stop following the diet?**	
	a) Intolerable i.e. did not like to foods, taste, diet	
	b) Side effects i.e. vomiting, diarrhoea, constipation	
	c) Completed the 3 month trial	
	d) Length of time on diet was too long	
	e) Extra hospital visits	
	f) Food costs	
	g) Found the diet too complicated to follow	
	h) Felt too unwell to continue	
	i) Other, please state:	
3.	**Did your weekly shop:**	
	a) Increase in price?	
	b) Decrease in price?	
	c) Stay the same price?	

Section 3		
1.	**Would you recommend a ketogenic diet to other glioma patients?**	**Tick**
	a) Yes	
	b) No	
2.	**If other patients with gliomas were to follow a ketogenic diet when would you suggest starting the diet?**	
	a) Before surgery (i.e. within a week of seeing your neurosurgeon)	
	b) After surgery (i.e. within 2 weeks to 3 months of discharge from hospital)	
	c) After surgery but before radiotherapy	
	d) After radiotherapy whilst receiving chemotherapy	
3.	**Would you recommend the ketogenic service at The Walton Centre to others?**	
	a) Yes	
	b) No	
	c) Unsure	
4.	**Did anything go particularly well?**	
5.	**Did anything not go well?**	
5.	**What could we do to improve our service?**	

Section 4		
1.	**Would you be interested in taking part in a clinical study to try and work out whether the diet can be delivered and is tolerable?**	
	a) Yes	
	b) No	
	c) Unsure	
2.	**If 'yes', would you still be interested in taking part in a study if half the people were given the diet and the other half received standard treatment?**	
	a) Yes	
	b) No	

	c) Unsure	
3.	**Would you be interested in taking part in a study which required you to try the ketogenic diet for longer than 12 weeks?**	
	a) Yes	
	b) No	
	c) Unsure	

Please write any additional comments below:

Thank you for completing this survey.

APPENDIX H: KEATING TRIAL PROTOCOL

Ketogenic Diets as an Adjuvant Therapy in Glioblastoma: A Randomised Pilot Study (The KEATING Trial)

Protocol

Version 4
20/12/2017

IRAS number: 218922

Ketogenic diets as an Adjuvant Therapy In Glioblastoma: A Randomised Pilot Study

Short title: The KEATING trial

Chief Investigator/Principle Investigator

Michael Jenkinson

Contact details: Institutions and Investigators

Sponsor (TBC)	**Chief Investigator and Academic Supervisor**
Alex Astor Head of Research Support – Health and Life Sciences University of Liverpool Research Support Office 2nd Floor Block D Waterhouse Building 3 Brownlow Street Liverpool, L69 3GL Email: sponsor@liv.ac.uk	Mr Michael D Jenkinson Clinical Senior Lecturer and Honorary Consultant Neurosurgeon The Walton Centre NHS Foundation Trust University of Liverpool Lower Lane Liverpool, L9 7LJ Tel +44 (0) 151 529 5683 (sec) Email: michael.jenkinson@liverpool.ac.uk
Investigator	**Statistician**
Prof Anthony G Marson Professor of Neurology The Walton Centre NHS Foundation Trust University of Liverpool Lower Lane Liverpool, L9 7LJ Tel +44 (0) 151 529 5770 (sec) Email: a.g.marson@liverpool.ac.uk	Dr Catrin Tudor-Smith Biostaistician Department of Biostatistics University of Liverpool Brownlow Hill Liverpool, L69 3BX Tel: +44 (0) 151 794 9754 Email: cat1@liverpool.ac.uk
Neuroradiologist	**PhD Student and Dietitian**
Dr Samantha Mills Consultant Neuroradiologist The Walton Centre NHS Foundation Trust University of Liverpool Lower Lane Liverpool, L9 7LJ Email: samantha.mills@thewaltoncentre.nhs.uk	Kirsty J Martin-McGill PhD Student Institute of Translational Medicine University of Liverpool Advanced Ketogenic Dietitian Therapies Department The Walton Centre NHS Foundation Trust Lower Lane Liverpool, L9 7LJ Tel: +44 (0) 151 529 5593 Email: kirsty.martin@liverpool.ac.uk
Investigator	
Dr Gemma Cherry Lecturer in Clinical Health Psychology University of Liverpool Brownlow Hill Liverpool, L69 3BX Email: Gcherry@liverpool.ac.uk	

Glossary of Abbreviations

AE	Adverse Event
ATRX	Alpha-thalassemia/mental retardation syndrome x-linked mutation
BMI	Body Mass Index
CI	Chief Investigator
CRF	Case Report Form
DH	Department of Health
EORTC	European Organisation for Research and Treatment of Cancer
FLAIR	Fluid-Attenuated Inversion Recovery
GB	Glioblastoma
GCP	Good Clinical Practice
GP	General Practitioner
HGS	Hand Grip Strength
HRA	Health Research Authority
IDH-1	Isocitrate Dehydrogenase 1
KD	Ketogenic Diet
LFT	Liver Function Test
MAMC	Mid Arm Muscle Circumference
MCT	Medium Chain Triglyceride diet
MDT	Multi-Disciplinary Team
MGMT	O^6-methylguanin-DNA-methyltransferase
MKD	Modified Ketogenic Diet
MRI	Magnetic Resonance Imaging
MUAC	Mid Upper Arm Circumference
NCRI	National Cancer Research Institute
NHS	National Health Service
NIHR	National Institute for Health Research
PENG	Parenteral and Enteral Nutrition Group
PPI	Patient and Public Involvement
QLQ	Quality of Life Questionnaire
RANO	Response Assessment in Neuro-Oncology
REC	Research Ethics Committee
SAE	Serious Adverse Event
SPSS	Statistical Package for Social Sciences
TSF	Tricep Skin Fold
WCFT	Walton Centre NHS Foundation Trust
WMA	World Medical Association

1. PROTOCOL SUMMARY

1.1 Population

This pilot study will be open to all Walton Centre NHS Foundation Trust (WCFT) patients with a newly diagnosed glioblastoma (GB), who have undergone surgical resection or biopsy and will go onto receive adjuvant oncological treatments.

1.2 Inclusion/exclusion criteria

The following criteria must be met by all proposed patients:

Inclusion criteria:

- Age ≥16 years
- Patient at WCFT
- Performance status ≤2 (Sørensen et al., 1993)
- Confirmed histological diagnosis of GB within last four months via surgical resection or biopsy (WHO grade IV, Louis et al., 2016)
- Will go onto receive or is currently receiving or completed adjuvant oncological treatments (radiotherapy, chemotherapy or combination radiochemotherapy)

Exclusion criteria:

- Having any prior use of a ketogenic diet (KD)
- Kidney dysfunction (CKD III/IV, renal stones, cancer, low phosphate/potassium/salt diets)
- Liver dysfunction (alcoholic liver disease, non-alcoholic liver disease, cancer, hepatitis, haemochromatosis, primary biliary cirrhosis)
- Gall bladder dysfunction (gall stones, cholecystectomy in past 12 months, cancer)
- Metabolic disorder (carnitine deficiencies, β oxidation defects [medium chain acyl-CoA dehydrogenase deficiency, long chain acyl-CoA dehydrogenase deficiency, short chain acyl-CoA dehydrogenase deficiency, long chain 3-hydroxyacyl CoA deficiency, medium chain 3-hydroxyacyl CoA deficiency], pyruvate carboxylase deficiency, porphyria)
- Eating disorder (anorexia nervosa, bulimia nervosa, binge eating disorder)
- Diabetes (requiring medication)
- Body mass index (BMI) ≤18.5kg/m^2

- Weight loss medications (Orlistat, Belviq, Contrave, Saxenda, Phentermine and Qsymia)
- Currently pregnant or breastfeeding
- Performance status ≥3 (Sørensen et al., 1993)
- Medical conditions that may increase risks associated with KD

1.3 Trial duration

The trial will recruit 12 patients over a 24 month period. Follow up will be for 12 months from the date the diet is commenced.

1.4 Description of intervention

A prospective, non-blinded, randomised, pilot study will be undertaken in patients with GB. Patients will be randomised to the modified ketogenic diet (MKD) or the medium chain triglyceride ketogenic diet (MCT) for a 12 week period (primary completion). If patients wish to remain on diet, they will be offered dietetic support as part of the trial for a total of 12 months (secondary completion). After this time, those who continue with the diet will have access to dietetic support and monitoring at 3 monthly intervals if they remain on diet.

1.5 Aim

To investigate protocol feasibility and patient impact by comparing two KDs in an NHS setting, with a view to inform the design of future phase III clinical trials.

1.6 Objectives

Primary objective:

- To estimate retention rate

Secondary objectives:

Protocol feasibility objectives

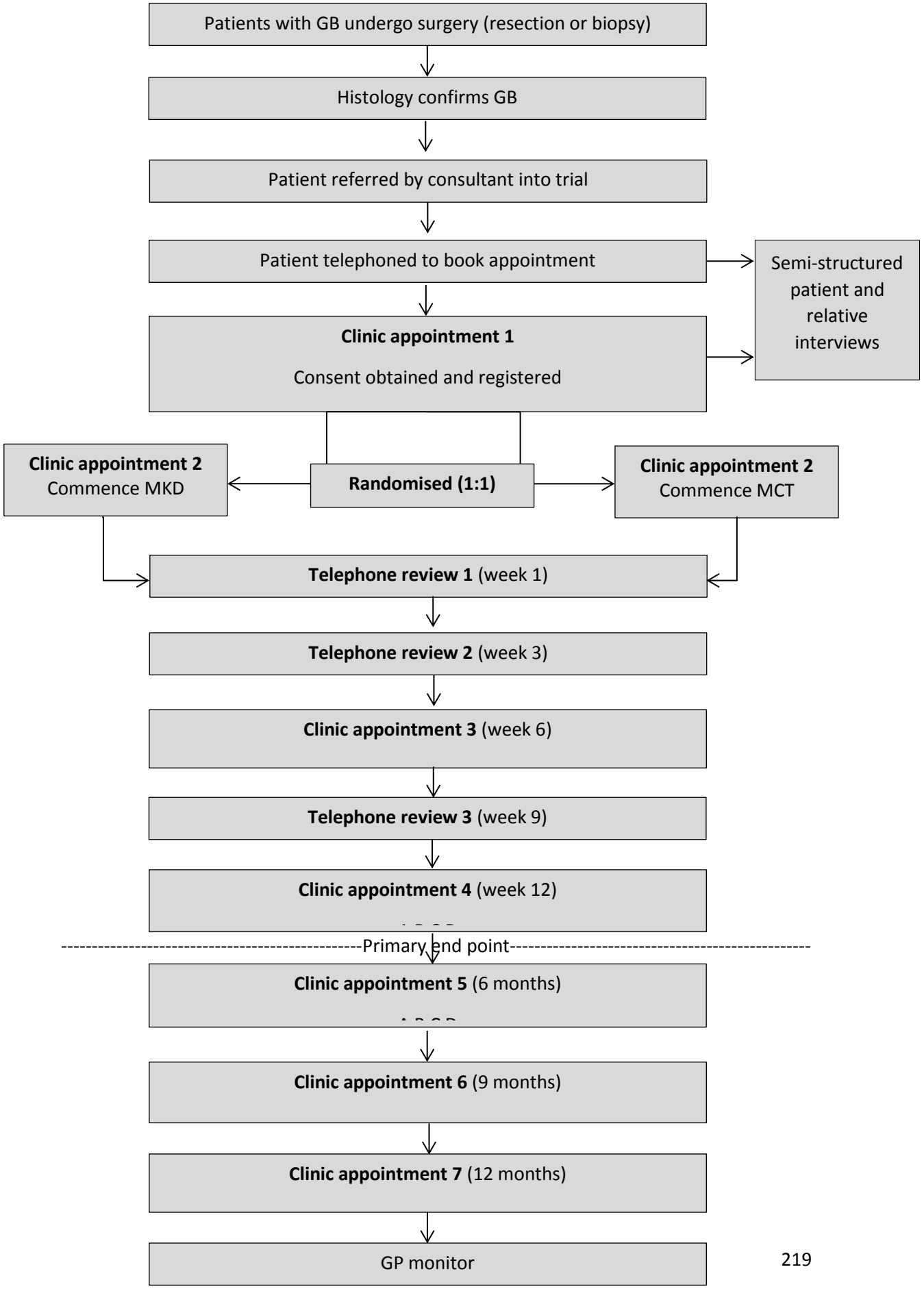
- To estimate recruitment rate
- To collect data about the enrolment of patients (consent, randomisation, baseline screening) pre oncological treatments
- To collect data about the enrolment of patients (consent, randomisation, baseline, screening) during oncological treatments

- To collect data about the enrolment of patients (consent, randomisation, baseline, screening) post oncological treatments (within four months of surgical intervention)
- To estimate long term retention
- To collect data about the dietary adjustments required to achieve ketosis
- To collect data about dietary compliance
- To collect data about MCT supplement compliance
- To collect data about ketosis levels
- To collect data about dietetic time required for each intervention
- To assess the protocol refinements required
- To collect data to inform sample size calculations of future trials
- Assess completeness of data for all trial outcomes

Patient impact objectives

- To collect data about quality of life
- To collect data about food acceptability
- To collect data about gastrointestinal side effects
- To collect data about changes in biochemical markers
- To collect data about anthropometric changes

1.7 Schematic of trial design



Key	
A	Anthropometry (weight, height, waist circumference, fat mass, body mass index [BMI], hand grip strength [HGS], mid arm muscle circumference [MAMC])
B	Biochemistry (renal, bone, liver function test (LFT), fasting lipid, fasting glucose)
C	Collect food and ketone diaries
D	Quality of life and food acceptability questionnaires

*Patients are able to telephone between appointments should further dietary support be required.

2. BACKGROUND

Glioblastoma (GB) is the commonest form of malignant brain tumour in adults, affecting 2-3 people per 100,000 per year (Radhakrishnan et al., 1995). Current treatment options include maximal safe resection, radiotherapy and temozolomide chemotherapy (Stupp et al., 2005). Despite these treatments, overall survival at two years is approximately 27%, with a median survival of 12-14 months (Krex et al., 2007). Over the last 10 years, several trials of newer chemotherapy agents (e.g. RTOG 0825 - Bevacizumab trial [Gilbert et al., 2014]) and targeted therapies (e.g. CENTRIC – Celengitide trial [Stupp et al., 2014]) has not improved the survival for patients with these tumours. Therefore, alternative treatment options are being explored and there is increasing interest in the possibility of using the ketogenic diet (KD) as an adjuvant treatment for patients with GB.

A KD is high in fat and low in carbohydrate, resulting in the production of ketones as a primary energy source, whilst minimising glycolysis through glucose restriction. Thus, as GBs are metabolically active tumours, they become deprived of their energy source. In animal models, implementing a KD as an adjuvant treatment has been shown to enhance survival (Woolf & Scheck, 2015), enhance radiotherapy sensitivity (Abdelwahab et al., 2012), improve chemotherapy signalling (Allen et al., 2013) and reduced peritumoural oedema (Jiang & Wang, 2013).

Recent studies investigating the use of the KD in humans have focused on the feasibility, safety and efficacy. However, at present, published evidence is based on case studies (Nebeling et al., 1995, Kalamian et al., 2008, Schwartz et al., 2015, Zuccoli et al., 2010) and one pilot trial (Rieger et al., 2014).

KDs can be unpalatable and their acceptability to patients with a short survival time has seen limited investigation so far (Rieger et al., 2014). There are various forms of the KD, with the two least restrictive being the modified ketogenic diet (MKD) and the medium chain triglyceride (MCT) KD. Both diets are currently used for treating paediatric epilepsy within

the National Health Service (NHS) and have proven efficacy in this settling (Neal et al., 2009 & Kossoff et al., 2006).

The MKD induces ketosis through encouraging a high fat and low carbohydrate intake, without limiting protein, fluid or energy intakes. There is no need for a fasting start or hospitalisation to commence the diet (Bergqvist et al., 2005). MKD is likely to be the more flexible and palatable of the KDs, therefore may be more suitable for adults undergoing oncological treatments.

MCT KD was first described by Huttenlocher et al. (1971) as a modification to the classic KD. It allows for the inclusion of larger portions of carbohydrate, thus, improving dietary tolerance and acceptability. A recent study by Martuscello et al. (2015) investigating the use of MCT KD in GB animal models found slower tumour progression, increased survival, increased body weight and positive changes to serum lipids in comparison to a standard KD and controls.

2.1 Rationale

Little is known about the palatability and acceptability of the KD in oncology patients with a limited survival time and suitable outcome measures have yet to be investigated.

We have recently completed feasibility work at The Walton Centre NHS Foundation Trust (WCFT) to investigate tolerance and acceptability of the MKD and the willingness of glioma patients to participate in clinical trials. The feasibility work comprised of:

1. A patient questionnaire (n=172)
2. A 3 month assessment of diet (n=6).

Sixty two percent of the questioned population (n=107) would like access to MKD. Sixty six percent (n=114) would be willing to trial the MKD for a 3 month period. Sixty percent of the population (n=104) would be willing to participate in a clinical trial, however if the trial involved randomisation between the diet and control (standard treatment + no diet) patient willingness to participate reduced to only 52% (n=54).

Six male GB patients received the MKD. Five patients tolerated the diet, found it acceptable, and subjectively reported improvements in quality of life. With regards to attrition, 1 patient dropped out after 4 weeks on diet due to local hospital admission and 1 patient after 6 weeks

due to dietary tolerance. Of the four patients who completed the 12 week trial all remain on diet, demonstrating the ability for the proposed trial to recruit and retain participants.

2.1.1 Patient and Public Involvement (PPI)

Patients from the feasibility project were invited to attend a PPI group. We sought their active involvement in identifying research priorities and outcome measures for KD in GB. Their opinion was also sought for improvements required to patient information leaflets, recruitment processes, clinic appointments and reducing patient costs to enhance trial participation. The ideas and opinions from the PPI group have been developed and incorporated into the protocol and supporting patient information sheets. The plain language summary for the proposed trial was approved by the PPI group.

2.2 Aim

To investigate protocol feasibility and patient impact by comparing two KDs in an NHS setting, with a view to informing future phase III clinical trials.

2.3 Objectives

Primary objective:

- To estimate retention rate

Secondary objectives:

Protocol feasibility objectives

- To estimate recruitment rate
- To collect data about the enrolment of patients (consent, randomisation, baseline screening) pre oncological treatments
- To collect data about the enrolment of patients (consent, randomisation, baseline, screening) during oncological treatments
- To collect data about the enrolment of patients (consent, randomisation, baseline, screening) post oncological treatments (within four months of surgical intervention)
- To estimate long term retention
- To collect data about the dietary adjustments required to achieve ketosis
- To collect data about dietary compliance
- To collect data about MCT supplement compliance
- To collect data about ketosis levels
- To collect data about dietetic time required for each intervention

- To assess the protocol refinements required
- To collect data to inform sample size calculations of future trials
- Assess completeness of data for all trial outcomes

Patient impact objectives

- To collect data about quality of life
- To collect data about food acceptability
- To collect data about gastrointestinal side effects
- To collect data about changes in biochemical markers
- To collect data about anthropometric changes

3.0 EXPERIMENTAL DESIGN AND METHODS

3.1 Trial design

A prospective, non-blinded, randomised, pilot study will be undertaken in patients diagnosed with GB. Patients will be randomised to receive the modified ketogenic diet (MKD) or medium chain triglyceride KD (MCT).

3.1.1 Primary end point

To assess retention and drop-out rates, defined as:

i. The number of patients who start randomised treatment as a proportion of the number randomised, with reasons for non-compliance.

ii. The number of patients who complete 12 weeks of diet as a proportion of the number randomised, with reasons for non-compliance.

iii. The time to dietary discontinuation (week 12 or duration to discontinuation if prior to this).

iv. Description of barriers and facilitators to data collection and participant retention.

3.1.2 Secondary end points

- Estimation of recruitment rates

Actual recruitment rates (over 24 months) will be compared to proposed recruitment figures (12 patients over 12 months) with purpose of demonstrating trial feasibility for future, potential phase III clinical trials.

- Enrolment of patients

Ability to comply with protocol enrolment time lines will be assessed by the number of patients initiated on diet prior to, whilst receiving, and post oncological treatment. This will inform the feasible time lines in future clinical trials.

- Long term retention

The time to dietary discontinuation after week 12.

- Dietary adjustments required to achieve ketosis

Dietary adjustments advised by the dietitian will be recorded in the case report form (CRF), to inform the macronutrient composition of the MKD and MCT diets required to achieve ketosis in this population to inform future protocols.

- Dietary compliance

Dietary compliance will be self-reported by the patient at clinic appointments. The dietitian will also analyse self-reported 3 day weighed food diaries (completed at weeks 6, 12 and every 3 months thereafter) using DietPlan 7© (nutritional analysis computer programme). The results will be compared to dietary fat and carbohydrate requirements (calculated at previous clinic appointment) and percentage compliance rates will be calculated.

- MCT compliance

MCT supplement compliance will be self-reported through 3 day weighed food diaries collected at week 6, week 12 and every 3 months thereafter. The results will be compared to the MCT dose advised (at previous clinic appointment) and a percentage compliance rate will be calculated.

- Ketosis levels

Ketosis will be monitored by patients self-reporting urinary ketones levels twice per day for the first 6 weeks then then once per week thereafter. Adequate urinary ketosis is defined as ≥4mmol/L. Blood ketones and blood glucose levels will be monitored weekly. Adequate blood glucose levels are defined as 3-5mmol/L. There are no robust guidelines for adequate levels of blood ketosis in adults with GB, however from preliminary work by Meidenbauer et al. (2015), levels of 2-4mmol/L to be beneficial, therefore patients will be asked to record

levels to aid future research. All figures will be recorded in the ketone diary provided. The dietitian will assess these at each point of contact.

- Dietetic time required for the interventions

Dietetic time spent on both clinical and non-clinical activities related to the trial will be recorded to aid future protocol design.

- Protocol refinements required

Deviations from the protocol will be documented on the deviation log. This will be used to refine future protocols and inform future clinical trials.

- Sample size estimates for future trials

Data synthesised from this pilot will inform sample size calculations for future phase III clinical trials, based on the primary outcome measure of retention.

- Quality of life

Quality of life will be evaluated though the EORTC QLQ C30 and QLQ BN 20 questionnaires prior to commencing the diet, at week 6, week 12 and every three months thereafter or at point of dietary discontinuation if prior to this.

- Food acceptability

Food acceptability will be assessed through the Food Acceptability Questionnaire (Barnard et al., 2009) completed prior to commencing the diet, at week 6, week 12 and every three months thereafter or at point of dietary discontinuation if prior to this.

- Gastrointestinal side effects

Gastrointestinal side effects will be quantified from the EORCT QLQ C30 questionnaire and through informal clinic assessments documented on CRF. The Common Terminology Criteria for Adverse Events ([CTCAE], version 4.0) will be used to grade gastrointestinal side effects documented on the CRF.

- Changes to biochemical markers

Biochemical markers (fasting lipid, fasting glucose, liver, renal and bone profiles) will be undertaken at baseline and repeated three monthly until discontinuation of diet.

- Anthropometric changes

Anthropometry (height, weight, body mass index (BMI), waist circumference, mid upper arm circumference (MUAC), mid arm muscle circumference (MAMC), tricep skin fold (TSF)[Body

Care, UK], hand grip strength (HGS) [Takei, Japan] and fat mass [Omron, Japan]) will be measured at baseline, week 6, week 12 and every three months thereafter. All measurements will be undertaken as per measurement methodology cited in Parenteral and Enteral Nutrition Group (PENG), pocket guide to clinical nutrition (Todorovic & Micklewright, 2011). See appendix 1 for details.

- Completeness of data for all trial outcomes

Completeness of documented data will be assessed to inform feasibility of future clinical trials.

Assistance permitted:

A carer/ relative may aid the patient in the completion diaries or questionnaires if required, with the patient's permission.

3.1.3 Defining pilot success

Pilot success will be graded using a traffic light system. The pilot will be deemed a success and progression to phase III trial will be considered appropriate if the following criteria are met:

Green (go):

- Recruitment rate of ≥75% of target (n=9) achieved within the 12 month recruitment period.
- ≥75% of patients commenced KD prior to chemoradiotherapy.
- Retention rate of ≥75% at 3 months.
- Diet acceptable to ≥75% of patients at 3 months.
- ≥75% of the proposed data collection completed for each end point.

Amber (review):

- Recruitment rate of ≥50% of target (n=6) achieved within the 12 month recruitment period.
- ≥50% of patients commenced KD prior to chemoradiotherapy.
- Retention rate of ≥50% at 3 months.
- Diet acceptable to ≥50% of patients at 3 months.
- ≥50% of the proposed data collection completed for each end point.

Red (stop):

- Recruitment rate <50% of target (n=5) achieved within the 12 month recruitment period.
- <50% of patients commenced KD prior to chemoradiotherapy.
- Retention rate of <50% at 3 months.
- Diet acceptable to <50% of patients at 3 months.
- <75% of the proposed data collection completed for each end point.

Retention rate, dietary acceptance and data collection will be assessed for each diet independently. Recruitment rate and dietary commencement will be assessed using data combined from both arms.

Any components of the pilot considered not feasible or unacceptable to patients will be evaluated prior to progression onto phase III clinical trial is considered. The Shanyinde et al. (2011) method will be used to categorise and assess the extent of the issue and the Bugge et al (2013) method will be used to evidence the decision making process.

3.2 Trial population

3.2.1 Population

The trial will be open to all WCFT patients with a newly diagnosed GB, who have undergone surgical resection and will go onto receive adjuvant chemoradiotherapy.

3.2.2 Inclusion/exclusion criteria

All patients considered for the trial must meet the following criteria:

Inclusion criteria

- Age ≥16 years
- Patient at WCFT
- Performance status ≤2 (Sørensen et al., 1993)
- Confirmed histological diagnosis of GB within last four months following surgical resection or biopsy (WHO grade IV, Louis et al., 2016)
- Will go onto receive, or is currently receiving, or completed adjuvant oncological treatments (radiotherapy, chemotherapy or combination chemoradiotherapy)

Exclusion criteria

- Having any prior use of a KD
- Kidney dysfunction (CKD III/IV, renal stones, cancer, low phosphate/potassium/salt diets)
- Liver dysfunction (alcoholic liver disease, non-alcoholic liver disease, cancer, hepatitis, haeochromatosis, primary biliary cirrhosis)
- Gall bladder dysfunction (gall stones, cholecystectomy in past 12 months, cancer)
- Metabolic disorder (carnitine deficiencies, β oxidation defects [medium chain acyl-CoA dehydrogenase deficiency, long chain acyl-CoA dehydrogenase deficiency, short chain acyl-CoA dehydrogenase deficiency, long chain 3-hydroxyacyl CoA deficiency, medium chain 3-hydroxyacyl CoA deficiency], pyruvate carboxylase deficiency, porphyria)
- Eating disorder (anorexia nervosa, bulimia nervosa, binge eating disorder)
- Diabetes (requiring medication)
- Body mass index (BMI) ≤18.5kg/m^2
- Weight loss medications (Orlistat, Belviq, Contrave, Saxenda, Phentermine and Qsymia)
- Currently pregnant or breastfeeding
- Performance status ≥3 (Sørensen et al., 1993)
- Medical conditions that may increase risks associated with KD

3.2.3 Identification of patients

Patients will be identified at WCFT neuro-oncology multi-disciplinary team (MDT) meeting; with documentation within MDT case sheet deemed an appropriate referral.

Patients will also be identified by neurosurgical consultants at WCFT clinics and referred in writing. Neuro-oncology nurses may also identify patients; however written referrals will be required from the consultant.

They will be approached for recruitment post resection or biopsy, once a histological diagnosis of GB is confirmed and a written referral is received from the consultant or MDT. The neurosurgical team has the option of providing patients with a patient information sheet in clinic. Patients will be contacted by the investigator by telephone to initially discuss the study and offered a screening appointment prior to commencing oncological treatments. They will receive a patient information sheet by post if not previously provided by the

neurosurgical team. Patients will receive a follow up phone call following initial oncological treatment as they also have the option of commencing diet within four months of initial surgical intervention.

3.3 Enrollment

3.3.1 Screening

Patients will be screened for eligibility at WCFT neuro-oncology MDT meeting or clinic.

A screening log will be maintained for all patients referred to the trial and reasons for ineligibility will be noted.

Enrolment will take place for 24 months from the date of opening.

3.3.2 Consent

Informed consent will be sought from all patients prior to enrollment. Through consenting to participate in the trial, patients will be consenting to dietary treatment, follow up and data collection.

3.3.3 Embedded Qualitative Information Study

A qualitative study will be embedded into KEATING, which will be referred to as the 'Information Study' in the patient information documents. The aim is to identify recruitment challenges and aid understanding of the patients' recruitment experience, by interviewing a sub-sample of patients and their relatives/ carers. Bespoke strategies will then be designed to optimise recruitment to future trials related to ketogenic diets and gliomas. This approach of embedded qualitative interviews has demonstrated success at optimising recruitment in previous trials (Mills et al. (2003), Donovan et al. (2002), Avery et al. (2014)), and will ensure patients are supported in making an informed decision about KEATING. Full details on the embedded qualitative information study can be found in Appendix 3.

3.3.4 Randomisation

Following consent and acquisition of baseline data, patients will be randomised into MKD or MCT groups after clinic appointment 1. The patients will be informed of diet group by telephone. A permuted block randomisation method will be adopted, using 'sealedenvelope'™ randomisation system. This will be set up and administered by the statistician, who is not involved with the recruiting of patients.

3.3.5 Baseline

Baseline data will be collected on the Case Report Form (CRF) at the initial consultation once eligibility is confirmed and consent obtained. Baseline data will include:

- Past medical history
- Symptoms at presentation
- Tumour location
- Surgical procedure
- Histopathology and molecular pathology subtypes for glioblastoma (MGMT, IDH-1, ATRX, 1p/19q status)
- Current medication (prescribed and purchased)
- Current nutritional supplementation (vitamins, minerals, herbal and nutritional products)
- Food allergies or intolerances
- Level of physical activity (as defined by DH, 1991)
- Food or fluid texture modification
- Use of enteral feeding tube
- Anthropometry (height, weight, BMI[ł], MUAC, TSF, MAMC, HGD, waist circumference and fat mass)
- Biochemistry* (fasting lipid, fasting glucose, liver, renal and bone profiles)
- Habitual 3 day weighed food diary
- Habitual gastrointestinal complaints
- Quality of life measures (EORTC QLQ C30 and QLQ BN 20 questionnaires)
- Habitual food acceptability (Food Acceptability Questionnaire)

ł BMI ≤18.5kg/m^2 at baseline assessment will result in exclusion from trial, as per exclusion criteria.

*Deranged biochemistry results may result in exclusion from the trial should the exclusion criteria be triggered. This will be at the discretion of the CI. Biochemistry results may take up to 24 hours to process, therefore if deranged resulting in trial exclusion, patients will be informed by telephone and appropriate follow up arranged if deemed to be required by the CI.

Histopathology and molecular pathology subtypes for glioblastoma (MGMT, IDH-1, ATRX, 1p/19q status) classification will be conducted as per the current standard of care.

MRI will be conducted as per the current standard of care for patients with GB (Jenkinson, 2011), resulting in scans at the following intervals:

- Pre surgery
- Post-surgery (within 72 hours)
- Pre radiotherapy
- 1 month post radiotherapy
- Mid chemotherapy (after 3 cycles)
- Post chemotherapy (after 6 cycles)
- Every 6 months from 12-24 months

MRI scans will include T1 ± gadolinium, T2 and fluid-attenuated inversion recovery (FLAIR) sequences. Extent of resection on post-operative MRI will be determined and recurrence will be measured according to the Response Assessment in Neuro-Oncology (RANO) criteria (Wen at al. 2010) and data collected on a supplementary CRF for monitoring of disease status.

Changes to medications and treatment will be recorded; these are permitted to be altered in-line with the treating oncologist/neurosurgeons recommendations. Details of concomitant radiotherapy and chemotherapy and adjuvant chemotherapy will be noted in the CRF.

3.3.6 Patient transfers

If the geographical distance moved is beyond what the patient is now willing to travel, then review should be conducted by telephone and post, with the patient's GP facilitating biochemistry collection. If this is not feasible the patient will be withdrawn from the trial.

3.3.7 Withdrawal from trial treatment

If there is a change in the patient's condition that in the clinician's opinion justifies dietary discontinuation or if the patient withdraws consent, the patient will be withdrawn from dietary treatment. In this case, data up until the point of withdrawal will be used in analysis. Unless the patient specifically withdraws consent further data will be gathered for progression free survival and overall survival analysis.

3.3.8 Withdrawal from trial completely

Patients will be made aware at the point of consent that they can withdraw at any time. No reason will be required. Should a patient withdraw, data will be included in the analysis until the point of withdrawal, unless the patient states otherwise. If they wish for their data to be excluded entirely, a CRF for destruction of data will be completed.

3.4 Trial treatments

3.4.1 Introduction

A prospective, non-blinded, randomised, pilot study will be undertaken in patients diagnosed with GB. Patients will be randomised to receive the modified ketogenic diet (MKD) or medium chain triglyceride KD (MCT).

3.4.2 Equipment and planning

Patients will be provided with the following when commencing the diet:

- FreeStyle Optimum Neo Blood Glucose and Ketone Monitoring System® (Abbott Diabetes Care, UK)
- Blood glucose strips (Abbott Diabetes Care, UK)
- Blood ketone strips (Abbott Diabetes Care, UK)
- Ketostix® (Bayer, Leverkusen, Germany)
- Urinary sample pot (NHS Supply, UK)
- Ketogenic diet prescription information sheet (diet specific)
- Food diary
- Food and MCT diary (if applicable)
- Urinary ketone diary
- Blood ketone and blood glucose diary
- Ketogenic recipes -modified for individual requirements and diet (Matthew's Friends, UK)
- Betaquik recipes – modified for individual requirements for those following MCT diet (Vitaflo International Ltd)
- 7 day individualised ketogenic diet plan

Patients will be instructed to check their urinary ketones twice per day for the first 6 weeks (upon wakening and 2 hours post evening meal), then twice per week thereafter (2 hours post evening meal, same days each week). Blood glucose and ketones will be tested weekly (2 hours post evening meal, same day each week). These figures will be recorded in the ketone diary provided. The dietitian will assess these at each point of contact.

The MCT supplement Betaquik ® (Vitaflo International Ltd, Liverpool, UK) is a ready to use liquid emulsion drink of MCT and will be supplied by Vitaflo International Ltd. Betaquik is nutritional supplement; therefore the quantity will be calculated by the investigator and

documented in the CRF. The manufacturing number and use by date of the supplements will also be documented in the CRF for traceability.

3.4.3 Definitions of targets

Adequate ketosis is defined as urinary ketones ≥4mmol/L (moderate ketosis is 4mmol/L, high ketosis 8-16mmol/L). Adequate blood glucose levels are defined as 3-5mmol/L.

3.4.4 Dietary calculations and reporting

MKD:

- Fat to provide 80% total energy requirements
- Carbohydrate to provide 5% of total energy requirements
- Protein allowed freely

MCT:

- Fat to provide 75% total energy requirements (30% total energy requirements from MCT fat)
- Carbohydrate to provide 10% of total energy requirements
- Protein allowed freely

Patients (and relatives when appropriate) will receive dietetic counseling and be provided with dietary literature to calculate intakes of these food groups. All patients will commence the diet at home, without a fasting start.

Energy requirements will be appropriate for patient's age, weight, activity and metabolic stress, monitored through weight checks. To estimate energy requirements a 3 day weighed food diary will be analysed using DietPlan 7© (Forestfield Software LTD, Horsham, UK) and compared to the PENG (Todorovic & Micklewright, 2011 [American Society of Parenteral and Enteral Nutrition, 2002, Barak et al., 2002, Department of Health, 1991, Henry, 2005, Hyltander et al., 1991, Knox et al., 1983]) energy requirements, from which a mean energy requirement should be estimated. The requirements can be tailed for weight loss, gain or maintenance dependent upon the patient's needs and wishes.

Dietary requirements will be recalculated each time a new weight is obtained.

Seven day diet plans will be calculated by the dietitian based upon total energy requirements. Nutritional content will be analysed using DietPlan 7© (Forestfield Software LTD, Horsham, UK) to ensure appropriate proportions of carbohydrate, fat and protein.

Patients will be required to complete a three day weighed food diary at baseline, 6 weeks and 12 weeks and every three months thereafter until discontinuation of diet.

Patients following the MCT diet will also be required to record intake of MCT within the food diary.

3.4.5 Timing

Patients have the option of commencing the diet within four months of surgical intervention (resection or biopsy). Patients may therefore commence diet prior to, during or post oncological intervention. All surgical and oncological interventions will be undertaken as per current standard of care.

3.4.6 Associated medications and treatments

Medications permitted: all medications with the exception of those specified below.

Medications not permitted: weight loss medications (including Orlistat, Belviq, Contrave, Saxenda, Phentermine and Qsymia) and any agents used in diabetic therapy (including Biguanides, Sulfonylureas, Meglitinide derivatives, Alpha-glucosidase inhibitors, Thiazolidinediones (TZDs), Glucagonlike peptide–1 (GLP-1) agonists, Dipeptidyl peptidase IV (DPP-4) Inhibitors, Selective sodium-glucose transporter-2 (SGLT-2) inhibitors, Insulins, Amylinomimetics, Bile acid sequestrants and Dopamine agonists).

Data will be collected on use of corticosteroids, antiemetics, laxatives and antiepileptic drugs. Data will also be collected for nutritional supplements consumed by the patient. All drugs prescribed for the patient will be recorded on the CRF.

3.4.7 Co-enrollment guidelines

Patients who have participated in and/or are enrolled on another trial may be eligible for the trial and should be discussed with the CI.

Patients enrolled on the trial may be eligible for other non-diet trials and involvement should be discussed with the CI.

Enrollments onto other trials involving diet or dietary supplements are not permitted.

3.5 Assessments and procedures

Baseline and follow up data will be collected on the CRF by the person named on the delegation log (the investigator).

The research site (WCFT) will maintain an investigator site file containing all essential trial documentation to allow for evaluation of trial conduct and data quality.

Table 1 illustrates assessments related to the trial.

Table 1: Assessments and time scales for the trial

Timeline		1 week post histology	1 week after clinic 1	1 weeks after clinic 2	3 weeks after clinic 2	6 weeks after clinic 2	9 weeks after clinic 2	12 weeks after clinic 2	6 months after clinic 2	9 months after clinic 2	12 months after clinic 2
Visit window	Post histology	± 5 days	±5 days	±3 days	±3 days	±5 days	±3 days	±5 days	±10 days	±10 days	±10 days
Clinic visit	Telephone and information sheet	Clinic appointment 1 Consent, register, baseline assessment, randomisation	Clinic appointment 2 Commence diet	Telephone review 1	Telephone review 2	Clinic appointment 3 Diet review	Telephone review 3	Clinic appointment 4 Diet review	Clinic appointment 5 Diet review	Clinic appointment 6 Diet review	Clinic appointment 7 Diet review End of trial
Informed consent		X									
Eligibility screen		X									
Randomisation		X									
Medical history review		X									
Medications review		X									
Anthropometry		X				X		X	X	X	X
Biochemistry		X						X	X	X	X
Food diary		X				X		X	X	X	X
Ketone diary						X		X	X	X	X
Quality of life (QoL) questionnaire EORCT QLQ C30		X				X		X	X	X	X
QoL questionnaire QLQ BN20		X				X		X	X	X	X
Food Acceptability Questionnaire		X				X		X	X	X	X
Dietary review		X	X	X	X	X	X	X	X	X	X
Ketone review				X	X	X	X	X	X	X	X

3.5.1 Procedures for assessing efficacy

Efficacy will not be determined from this trial due to limitations in sample size. However, MRI will be used to interpret tumour progression and progression free survival for those patients enrolled on the trial. MRI will be conducted as per the current standard of care for patients with GB and will include the following sequencing; T1 ± gadolinium, T2 and FLAIR (see enrolment).

Progression free survival will be defined as the time from date of randomisation to date of recurrence on MRI. Recurrence will be as defined by a Neuroradiologist using the RANO criteria (Wen et al., 2010). All scans will be undertaken as per current standard of care. No additional imaging will be required. Progression free survival data will then be assessed by Kaplan-Meier survival analysis.

Overall survival will be defined as the time from date of randomisation to date of death from any cause.

This information will be recorded in a supplementary CRF for monitoring of disease status, as will be completed by the Neuroradiologist.

3.5.2 Procedures for assessing safety

Adverse events associated with the diet will be recorded in the CRF (see safety reporting).

3.5.3 Loss to follow up

Reasons for loss to follow up will be recorded on CRF.

3.5.4 Trial closure

There is a 24 month recruitment period, followed by a 12 month trial period (maximum), therefore the trial will close 12 months after the enrollment of the final patient, to allow sufficient time for data analysis. The trial would close early should serious adverse events occur as a direct result of the trial intervention, which would be advised by the Sponsor.

3.6 Statistical considerations

3.6.1 Sample size

Feasibility data demonstrates a likely retention rate of 70% participants at 12 weeks. With a sample size of 12 we will be able to estimate retention rates of 70% to within a 95% confidence interval of ±25.93% (Hooper, no date). Billingham et al. (2013) demonstrate a median sample size of 30 (range 8-114 participants) for UK pilot studies, whilst Hertzog (2008) reports on the statistical adequacy for sample sizes of 10-40, thus further justifying a sample size of 12 for the current trial.

Recruitment time is a limiting factor to sample size. Given the recruitment window and our previous feasibility work demonstrating a patient recruitment figure of 1 per month, a sample size of 12 as specified above, should be achievable.

Cost of resources is also a limiting factor to sample size, given the implications of ketone monitoring on resources (see section 7.1).

Data synthesised from this pilot will inform sample size estimates for future, phase III clinical trials.

3.6.2 Analysis plan

A detailed analysis plan will be developed prior to the final analysis. In brief, descriptive statistics will be used to summarise retention, recruitment rates, enrolment adherence, dietary adjustments, dietetic time, dietary compliance, MCT supplement compliance, ketosis, anthropometry changes, biochemistry changes, quality of life, food acceptability and gastrointestinal side effects. The Kaplan-Meier survival curve will be estimated for overall survival and progression free survival and displayed graphically with 95% confidence intervals.

3.7 Safety reporting

3.7.1 Terms and definitions

Adverse event (AE): is any unexpected situation that takes place during the course of the trial. An AE may be related to the dietary intervention or an unrelated cause.

Serious adverse event (SAE): an event which results in death, is life threatening, requires hospital admission or prolongs hospital stay, results in significant or persistent disability or incapacity or results in a birth defect.

Life threatening: potentially fatal illness or injury at time of occurrence.

Related: resulted from the administration of the dietary intervention.

Unexpected: type of AE or SAE not listed on the protocol and is not a likely occurrence.

3.7.2 Adverse event inclusions and exclusions

Inclusion:

- Injury or accident
- Abnormalities in biochemistry that require further investigation or treatment
- Exacerbation of a pre-existing illness

- Development of an illness during the trial
- Worsening of baseline symptoms

Exclusion:

- Previously planned hospital admission
- Past medical conditions that do not worsen with intervention
- Medical or surgical procedures undertaken due to the adverse event
- Elective cosmetic surgery
- Gastrointestinal side effects unless resulting in hospital admission
- Altered lipid profiles unless resulting in the commencement of lipid lowering medication or further investigations

The Common Terminology Criteria for Adverse Events ([CTCAE], version 4.0) will be used to grade AEs.

All deaths occurring from recruitment to end of follow up will be reported to the Heath Research Authority (HRA) Research Ethics Committee (REC).

3.7.3 Pregnancy

The effects of KD on pregnancy are unknown; therefore pregnancy is an exclusion criterion for the trial. Should a patient become pregnant the dietary intervention will be discontinued, the patient will receive the appropriate dietary counseling for pregnancy and appropriate obstetric care will be arranged.

3.7.4 Severity of adverse events

The National Institute for Health Research (NIHR) 'decision tree for adverse event reporting' will be used to grade AE and SAE severity (see appendix 2).

An AE or SAE will be reported by the investigator; however the CI will be responsible for determining causality. The CI will use clinical judgment to determine causality, the result of which will be documented on the SAE form.

3.7.5 Expectedness

A summary of expected adverse events related to KD and compiled from relevant literature (Martin et al., 2016) are as follows:

- Gastrointestinal intolerance (such as diarrhoea, constipation, nausea, reflux, abdominal discomfort)
- Altered or raised cholesterol
- Kidney stones
- Decreased bone density

Other risks reported in low numbers include:

- Anorexia
- Lethargy
- Lower respiratory tract infections
- Hyperammonaemic encephalopathy

Other risks reported in low numbers, with KDs of a higher dietary fat content, include:

- Infectious disease (pneumonia and sepsis)
- Acute pancreatitis
- Gallstones
- Fatty liver
- Nephrocalcinosis
- Status epilepticus, acidosis
- Dehydration
- Tachycardia
- Hunger

A summary of expected adverse events related to tumour are as follows:

- Headache
- Numbness to limbs
- Seizures
- Cognitive decline
- Mood and personality changes
- Mobility decline
- Nausea

- Vomiting
- Disordered speech, vision or hearing

A summary of expected adverse events related to radiotherapy are as follows:

Short term events (≤3 months post radiotherapy)

- Scalp erythema
- Wound breakdown
- Alopecia
- Headache
- Nausea
- Fatigue
- Seizures

Long term events (>3 months post radiotherapy)

- Cognitive decline
- Pituitary dysfunction
- Leucoencephalopathy

A summary of expected adverse events related to chemotherapy (Temozolmide) are as follows:

- Alopecia
- Fatigue
- Constipation
- Diarrhoea
- Skin rash
- Dizziness
- Blurred vision
- Insomnia
- Taste changes

More severe side effects of chemotherapy (Temozolomide) include:

- Decreased bone marrow function

3.7.6 Follow up after adverse events

All AE or SAE will be followed up until a satisfactory outcome is obtained or the patient is deemed to be stable by the CI.

3.7.7 Responsibilities – investigator

The investigator is responsible for informing REC of related and unexpected SAE. These will be sent within 15 days of the CI becoming aware of the event. The HRA SAE report form will be used (http://www.hra.nhs.uk/resources/during-and-after-your-study/nhs-research-ethics-committee-rec-ctimp-safety-report-form/) and emailed to (HRA.Queries@nhs.net).

The CI may take appropriate urgent safety measures without prior contacting the REC. However, the REC will be contacted by telephone immediately and within 3 days in writing should a change to protocol occur.

3.7.8 Responsibilities - REC

The REC manager will acknowledge receiving all safety reports within 30 days by signing and returning a copy of the cover form.

3.7.9 Safety reports

A progress safety report will be submitted to REC annually by the CI or delegate and must be signed by the CI.

The NHS REC annual progress report from can be located from the HRA website: http://www.hra.nhs.uk/resources/during-and-after-your-study/nhs-rec-annual-progress-report-forms/

3.7.10 Contact details and out of hours cover

This trial is considered low risk and a low proportion of SAE are expected. The dietetic investigator will be the primary contact. Out of hours cover will be provided in line with routine clinical care. In the event of additional clinical advice being required, the CI will be contacted. Contact details can be found in section 10.

3.8 Data management

The CI is responsible for ensuring appropriate conduct at the site.

3.8.1 Data recording

The investigator will document all activities at each trial visit, in the patient's medical notes. This data will be recorded using source documents to standardise assessments and activities.

All data collected from the source documents will be pseudo anonymised. Essential trial paper documentation (food diaries, ketone diaries, food acceptability questionnaires, EORTC QLQ C30 and BN20 questionnaires) and the CRFs (main and supplementary CRF) will include a trial number. Computer data sets will only contain the trial number. The original paper copy of the trial documents will be held in the main CRF.

Nutritional analysis will be conducted using DietPlan 7© (Forestfield Software LTD, Horsham, UK). All data will be anonymised prior to analysis using the programme. No data will be stored on this programme due to data protection. All nutritional analysis will be printed, assigned with the appropriate trial number and the original copy will be stored in the main CRF.

A letter to summarise dietetic care and intervention at each appointment will be addressed to the referring consultant as per routine dietetic care, a copy of which will be sent to the GP and CI. In addition for trial purposes one copy will be held in the medical notes and one in the main CRF.

The investigator has primary responsibility for ensuring accurate and timely completion of clinic source documents and letters (within 24 hours of assessment).

3.8.2 Data storage

Data will be pseudo anonymised and transferred onto a password protected electronic spreadsheet (Microsoft Excel©) held on University of Liverpool Active DataStore. No identifiable information such as hospital number, NHS number or name will be held on the database or used in the dissemination of results. Patient data within the database will be identified with a unique trial number which will relate back to the CRFs.

The investigator has primary responsibility for ensuring accurate and timely completion of the spreadsheet (within 7 working days of data collection).

As this is a trial, clinic bookings cannot be made on the WCFT booking system. Therefore a password protected Microsoft Excel© spreadsheet will hold data relating to clinic appointments, accessed only through a WCFT computer network. Appointment letters sent to patients will also be held within a password protected file, accessed only through a WCFT computer. Approval for this has been sought from the Assistant Divisional General Manager and Research, Development and Innovation Manager of WCFT.

The CRFs and all other paper trial documentation will be held in a lockable filing cabinet for the duration of the trial, within the Dietetic Office, at WCFT. Medical notes in use will be tracked to and held in a lockable filing cabinet, within the Dietetic Office, at WCFT and then returned to the Health Records Library at WCFT when no longer required, as per the WCFT Clinical Records Management Policy.

3.8.3 Records retention

Data will be held for 10 years to allow for future retrospective comparisons to larger scale studies. After the trial is complete, the essential trial paper documentation and CRFs will be archived by the University of Liverpool Records Management Department and held at University Records Centre, 150 Mount Pleasant, Liverpool, L69 3GD. Electronic data will be archived by the investigator, in the University of Liverpool Data Catalogue, as per the University of Liverpool, Research Data Management Policy. Source documents are held within the medical notes, therefore are retained in the Health Records Library of WCFT, as per the WCFT Clinical Records Management Policy.

Data will be archived with the permission of the CI, who is the custodian.

3.4 Indemnity

The student investigator has indemnity cover provided by the British Dietetic Association. The University of Liverpool as sponsor holds insurance for injury caused by participation in a clinical trial. The WCFT is an NHS trust, thus has a duty of care to its patients and a legal liable for acts of negligence by their employees, which includes those patients participating in the trial.

5. ETHICAL CONSIDERATIONS

The World Medical Association (WMA) of Helsinki, ethical principles for medical research involving human subjects, and amendments up to and including Fortaleza (2013) will be abided by.

HRA REC approval will be sought for this pilot study, involving NHS patients with GB for MKD dietary interventions. Protocol approval will also be sought from WCFT research, development and innovation department. Approval for patient information sheets will be sought from HRA REC and Patient Information Panel at WCFT prior to being provided to patients.

Ethical approval will be overseen by the CI. The University of Liverpool will be the pilot study sponsor.

Data will be recorded using Microsoft Excel© and statistical analysis undertaken using Statistical Package for Social Sciences (SPSS©).

5.1 Informed consent

Patients will receive sufficient information and will be given sufficient time to consider participation in the trial. They will be able to discuss their involvement with family members if required. The investigator will comply with Good Clinical Practice (GCP) consent guidelines and WMA ethical principles.

Patients will be referred to the study by written correspondence from the treating consultant. Patients will be telephoned by the investigator to receive an appointment to discuss the trial and potential recruitment.

A trial information leaflet will be provided and discussed with all potential patients. The information sheet will explain the purpose of the study, voluntary participation, methodology, advantages and disadvantages of participation, confidentiality, result dissemination, right to withdraw and funding providers. The leaflet will also provide a point of contact should the patient require further information.

Those willing to participate will be asked to sign a consent form. A copy of the consent form will be given to the patient, one copy will be held in the CFR and the original will be placed in the patient's medical notes, along with a copy of the trial information sheet.

Ongoing willingness to participate in the trial will be sought each time the patient is seen by an investigator and documented in the medical notes.

No explanation will be sought from those patients who do not wish to participate in the trial. However, should an explanation voluntarily be provided, a record of this will be kept to inform trial feasibility.

5.2 Trial discontinuation

Patients who discontinue the trial early will be provided with a patient information sheet containing information on how to discontinue the diet. They will then be followed up according to routine clinical care. Their GP and treating consultant will be informed in writing. For those patients alive after trial closure who wish to continue with the diet, dietetic review and monitoring will continue at 3 monthly intervals until dietary discontinuation.

6. RISKS AND BENEFITS OF THE TRIAL

6.1 Risks

Known side effects from the KD include gastrointestinal intolerance (such as diarrhoea, constipation, nausea, reflux, abdominal discomfort), altered or raised cholesterol, kidney stones and decreased bone density. Other risks reported in low numbers include anorexia, lethargy, lower respiratory tract infections and hyperammonaemic encephalopathy. Other risks reported in low numbers, with KDs of a higher dietary fat content, include infectious disease (pneumonia and sepsis), acute pancreatitis, gallstones, fatty liver, nephrocalcinosis, status epilepticus, acidosis, dehydration, tachycardia and hunger (Martin et al., 2016).

6.2 Benefits

There are no known potential benefits for patients participating in the trial. This is a pilot study to establish protocol feasibility and dietary impact to patients. The sample size will be too small to draw conclusions for efficacy.

7. RESOURCES

7.1 Resources

7.1.1 Ketone monitoring

- Blood ketone monitor
- Blood glucose strips
- Blood ketone strips
- Ketostix® (Bayer, Leverkusen, Germany)
- Urinary sample pot (NHS Supply, UK)

7.1.2 Anthropometry monitoring

- Disposable tape measures (Spentex BCA Ltd, UK)
- Plastic calipers (Body Care, UK)
- Hand grip dynamometer, T.K.K. 5401 (Takei Scientific Instruments Ltd, Japan)
- Body fat monitor, BF306 (Omron Healthcare Co. Ltd, Japan)

7.1.3 Patient information sheets

- Study information sheet and consent
- Ketogenic diet prescription (diet specific)
- Food diary
- Food and MCT diary (if appropriate)

- Urinary ketone diary
- Blood ketone and blood glucose diary
- Ketogenic recipes (Matthew's Friends, UK)
- Betaquik recipes (Vitaflo International Ltd, UK)
- 7 day individualised ketogenic diet plan
- Discontinuing the MCT diet
- Discontinuing the MKD
- Quality of life questionnaire EORTC QLQ C30
- Quality of life questionnaire QLQ BN 20
- Food Acceptability Questionnaire

7.1.4 Biochemistry

- Blood forms

8. RESEARCH REGISTRATION

The trial will seek registration from ClinicalTrials.gov and will seek portfolio adoption from the National Cancer Research Institute (NCRI) Brain Tumour clinical studies group.

9. DISSIMINATION

The trial will be undertaken as part of a PhD programme at the University of Liverpool. Completion of a thesis is proposed for July 2019.

Results of the trial will be published as soon as possible, in an appropriate peer reviewed journal and presented at appropriate conferences. The financial sponsor Vitaflo International Ltd will be acknowledged, however they will have no part in conducting or analysing the trial.

A newsletter detailing the findings of the trial will be circulated to those patients who are alive at time of completion, if the patient previously consented to receiving such information.

10. TRIAL INFORMATION

As this trial is being undertaken as part of a PhD programme at the University of Liverpool, the student will act as investigator and the academic supervisor as CI.

11. REFERENCES

Abdelwahab MG, Fenton KE, Preul, MC, et al. (2012). The ketogenic diet is an effective adjuvant to radiation therapy for the treatment of malignant glioma. *PLos One, 7*(5):e36197.

Allen BG, Bhatia SK, Buatti JM, et al. (2013). Ketogenic diets enhance oxidative stress and radiochemotherapy response in lung cancer xenografts. *Clinical Cancer Research, 19*(14), 3905-3913.

American Society of Parenteral and Enteral Nutrition Board of Directors and the Clinical Guidelines Task Force. (2002). Guidelines for the use of parenteral and enteral nutrition in adult and pediatric patients. *Journal of Parenteral and Enteral Nutrition, 26*, suppl 1.

Avery KNL, Donovan JL, Horwood J, et al. (2014). The importance of dietary change for men diagnosed with and at risk of prostate cancer: a mutlicentre interview study with men, their partners and health care professionals. *BMC Family Practice, 15*(81).

Barak N, Wall-Alonso E, Sitrin MD. (2002). Evaluation of stress factors and body weight adjustments currently used to estimate energy expenditure in hospitalised patients. *Journal of Parenteral and Enteral Nutrition*, *26*(4), 231-238.

Barnard ND, Gloede L, Cohen J, et al. (2009). A low-fat vegan diet elicits greater macronutrient changes, but is comparable in adherence and acceptability, compared with more conventional diabetes diet among individuals with type 2 diabetes. *Journal of the American Dietetic Association, 109*, 263-272.

Bergqvist AGC, Schall JI, Gallagher PR, Cnaan A, Stallings VA. (2005). Fasting versus gradual initiation of the ketogenic diet: a prospective, randomized clinical trial of efficacy. *Epilepsia, 46*(11), 1810-1819.

Billingham SAM, Whitehead AL, Julious SA. (2013). An audit of sample sizes for pilot and feasibility trials being undertaken in the United Kingdom registered in the United Kingdom Clinical Research Network database. *BMC Medical Research Methodology, 13*:104.

Braun V, Clarke V. (2006). Using thematic analysis in psychology. *Qualitative Research in Psychology, 3*(2), 77-101.

Bugge C, Williams B, Hagen S, et al. (2013). A process for Decision-making after Pilot and feasibility Trials (ADePT): development following a feasibility study of a complex intervention for pelvic organ prolapse. *Trials, 14*, 353-366.

Department of Health. (1991). Dietary reference values for food energy and nutrients for the United Kingdom. HMSO, London.

Donovan J, Mills N, Smith M, et al. (2002). Improving design and conduct of randomized trials by embedding them in qualitative research: ProtecT (prostate testing for cancer and treatment) study. *BMJ, 325*, 766-770.

Gilbert MR, Dignam JJ, Armstrong TS, Wefel JS, Blumenthal DT, et al. (2014). A randomized trial of Bevacizumab for newly diagnosed glioblastoma. *The New England Journal of Medicine, 370*(8), 699-708.

Goel MK, Khanna P, Kishore J. (2010). Understanding survival analysis: Kaplan-Meier estimate. *International Journal of Ayurveda Research, 1*(4), 274-278.

Harrop E, Kelly, J, Griffith, G et al. (2016). Why do patients decline surgical trials? Findings from a qualitative interview study embedded in the Cancer Research UK BOLERO trial (Bladder cancer: Open versus Laparoscopic or Robotic cystectomy). *Trials, 17*(35).

Henry CJK. (2005). Basal metabolic rate studies in humans: measurement and development of new equations. *Public Health Nutrition, 8*(7a), 1133-1152.

Hertzog MA. (2008). Considerations in determining sample size for pilot studies. *Research in Nursing and Health, 31*(2), 180-191.

Hooper R. (no date). *Justifying sample size for a feasibility study*. Research design service. Queen Mary, University of London. London.

Hubbard G, O'Carroll R, Munro j, et al. (2016). The feasibility and acceptability of trial procedures for a pragmatic randomised controlled trial of structured physical activity intervention for people diagnosed with colorectal cancer: findings from a pilot trial of cardiac rehabilitation versus usual care (no rehabilitation) with an embedded qualitative study. *Pilot and Feasibility Studies, 2*(51).

Huttenlocher PR, Wilbourne AJ, Sigmore JM. (1971). Medium chain triglycerides as a therapy for intractable childhood epilepsy. *Neurology, 21*, 1097-1103.

Hyltander A, Drott C, Korner ID, et al. (1991). Elevated energy expenditure in cancer patients with solid tumours. *European Journal of Cancer, 27*(1), 9-15.

Jenkinson, MD. (2011). *High grade glioma guidelines*. Merseyside and Cheshire Neuro-oncology Clinical Network Group. Liverpool, UK.

Jiang YS, Wang FR. (2013). Caloric restriction reduces edema and prolongs survival in a mouse glioma model. *Journal Neurooncology, 114,* 25-32.

Julious SA. (2005). Sample size of 12 per group rule of thumb for a pilot. *Pharmaceutical Statistics, 4*(4), 287-291.

Kalamian M, Zupec-Kania B, Favara BE, Liepa GU. (2008). Ketogenic diet as an adjuvant therapy for brain tumors. *First international symposium on the ketogenic diet for epilepsy and other neurological disorders*. Barrows Neurological Institue, Phoenix, Arizona: Poster presentation.

Knox LS, Crosby LO, Feurer ID, et al. (1983). Energy expenditure in malnourished cancer patients. *Annals of Surgery, 197*(2), 152-162.

Kossoff EH, McGrogan JR, Bluml RM, Pillas DJ, Rubenstein JE, Vining EP. (2006). A modified Atkins diet is effective for the treatment of intractable pediatric epilepsy. *Epilepsia, 47*, 421-424.

Kossoff EH, Turner Z, Bluml RM, Pyzik PL, Vining, EPG. (2007). A randomized, crossover comparison of daily carbohydrate limits using the modified Atkins diet. *Epilepsy & Behavior, 10*, 432-436.

Krex D, Klink B, Hartmann, et al. (2007). Long term survival with Glioblastoma multiforme. *Brain, 130*(10), 2596-2606.

Louis DN, Perry A, Reifenberger G, von Deimling A, Figarella-Branger D, et al. (2016). The 2016 World Health Organization classification of tumours in the central nervous system. *Acta Neuropathologica, 131, 803-820.*

Martin K, Jackson CF, Levy RG, Cooper PN. (2016). Ketogenic diet and other dietary treatments for epilepsy. Cochrane Database of Systematic Reviews 2016, Issue 2. Art. No.: CD001903. DOI: 10.1002/14651858.CD001903.pub3.

Martuscello RT, Vedam-Mai V, McCarthy DJ, et al. (2015). A supplemented high-fat low-carbohydrate diet for the treatment of Glioblastoma. *Clinical Cancer Research,* e-publication. DOI: 10.1158/1078-0432.CCR-15-0916.

Mills N, Donovan JL, Smith M, et al. (2003). Perceptions of equipoise are critical to trial participation: a qualitative study of men in the ProtecT study. *Controlled Clinical Trials, 24*, 272-282.

Moore CG, Carter RE, Nietert PJ, et al. (2011). Recommendations for planning pilot studies in clinical and translational research. *Clinical and Translational Research, 4*(5), 332-337.

Murphy E, Dingwall R, Greatbatch D, et al. (1998). Qualitative research methods in health technology assessment: a review of literature. *Health Technology Assessment, 2*(16), 1-274.

National Institute of Health Research: Clinical Research Network. (2016). Decision Tree for Adverse Event Reporting. Accessed on 13th July 2016, from https://www.crn.nihr.ac.uk/wp-content/uploads/Learning%20and%20development/Decision%20Tree%20for%20Adverse%22Event%20Reporting.pdf

Neal EG, Chaffe H, Schwartz RH, Lawson MS, Edwards N, et al. (2009). A randomized trial of classical and medium chain triglyceride ketogenic diets in the treatment of childhood epilepsy. *Epilepsia, 50*(5), 1109-1117.

Nebeling LC, Miraldi F, Shurin SB, et al. (1995). Effects of ketogenic diet on tumor metabolism and nutritional status in pediatric oncology patients: two case reports. *Journal of the American College of Nutrition, 14*(2), 202-208.

Poston L, Briley AL, Barr S, et al. (2013). Developing a complex intervention for diet and activity behavour change in obese pregnant women (UPBEAT trial); assessment of behavior change and process evaluation in a pilot randomised controlled trial. *BMC Pregnancy and Childbirth, 13*(148).

Radhakrishnan K, Mokri B, Parisi JE, et al. (1995). The trends in incidence of primary brain tumors in the population of Rochester, Minnesota. *Annals of Neurology, 37*, 67-73.

Rieger J, Bahr O, Maurer GD, et al. (2014). ERGO: a pilot study of ketogenic diet in recurrent glioblastoma. *International Journal of Oncology, 44*, 1843-1852.

Schwartz K, Chang HT, Nikolai M, et al. (2015). Treatment of glioma patients with ketogenic diets: report of two cases treated with an IRB-approved energy-restricted ketogenic diet protocol and review of the literature. *Cancer and metabolism, 3*(3), 1-10.

Seale C. (1999). The quality of qualitative research. London: Sage.

Shanyinde M, Pickering RM, Weatherall M. (2011). Questions asked and answered in pilot and feasibility randomized control trials. *BMC Medical Research Methodology, 11*, 117-128.

Sørensen JB, Klee M, Palshof T, et al. (1993). Performance status assessment in cancer patients. An inter-observer variability study. *British Journal of Cancer, 67*(4), 773-775.

Stupp R, Mason WP, van den Bent MJ, Weller M, Fisher B, et al. (2005). Radiotherapy plus concomitant and adjuvant temozolomide for glioblastoma. *The New England Journal of Medicine, 352*, 987-996.

Stupp R, Hegi ME, Gorlia T, Erridge SC, Perry J, et al. (2014). Cilengitide combined with standard treatment for patients with newly diagnosed glioblastoma with methylated MGMT promoter (CENTRIC EORTC 26071-22072 study): a multicentre, randomised, open-label, phase 3 trial. *The Lancet Oncology, 15*(10), 1100-1108.

Todorovic VE & Micklewright A. (2011). *A pocket guide to clinical nutrition*. The Parenteral and Enteral Nutrition Group of the British Dietetic Association (4th Ed.). Birmingham, UK.

Wen PY, Macdonald DR, Reardon DA, Cloughesy TF, Sorensen AG, et al. (2010). Updated response assessment criteria for high-grade gliomas: Response Assessment in Neuro-Oncology Working Group. *Journal of Clinical Oncology, 28*(11), 1963-1972.

White C, Hardy J. (2010). What do palliative care patients and their relatives think about research in palliative care? – a systematic review. Support Cancer Care, 18, 905-911.

Woolf EC, Scheck AC. (2015). The Ketogenic diet for the treatment of malignant glioma. *Journal of Lipid Research, 56*(1), 5-10.

Zuccoli G, Marcello N, Pisanello A. (2010). Metabolic management of glioblastoma multiforme using standard therapy together with a restricted ketogenic diet: Case report. *Nutrition and metabolism, 7*(33), 1-7.

PROTOCOL APPENDIX 1: ANTHROPOMETRY METHODOLOGY

Height

- Use a stadiometer.
- The patient is to stand with their back to the measure.
- Reading should be taken from the top of the head, when the patient is looking directly ahead.

Weight

- Use Marsden (M-520) freestanding digital weighing scales.
- Patient to stand on scales, independently (without holding objects that would affect reading).

Body Mass Index (BMI)

- Weight (kg)/ height (m^2).

Mid arm muscle circumference (MUAC)

- The patient should be sitting.
- Use the left arm, bare of clothing.
- Locate the acromion and olecranon process.
- Use a disposable paper tape measure to measure the distance between the two points.
- Identify the midpoint and measure the circumference of the arm at this point.

Tricep skinfold

- The patients left arm should be in a relaxed position.
- Locate the midpoint identified in the MUAC measurement.
- Raise the skin by pinching the skin, to obtain a double layer of skin and the underlying adipose tissue.
- Standing behind the patient's left arm, apply the caliper (Body Care, UK) at a right angle to the fold.
- Repeat measure 3 times.

Mid arm muscle circumference (MAMC)

- MAMC (cm) = MAUC (cm) – (3.14 x TSF [cm]).
- Note the conversion of TSF from mm to cm.

Hand grip dynamometry

- Takei (Japan) hand grip dynamometer should be used.
- Non-dominant arm, standing and elbow of the arm extended.
- Can be taken from a sitting position with elbow at 90^{o} angel, but the difference in method should be documented and consistently repeated.
- Patient to compress dynamometer handle.
- The mean of 3 measures should be documented.

Fat mass (bio electronic impedance analysis)

- Measured using the Omron (Japan) body fat mass hand held machine.
- Input height, weight, age and gender.
- Patient to grip machine in both hands on the metal discs in a seated position, with arms straight out in front at a right angle to the body.
- Measurement should be undertaken a minimum of two hours after food or fluid, where possible.
- BIA should not be undertaken in patients with a pacemaker or those who are pregnant.

Waist circumference

- The patient should be standing.
- The measurement should be taken at the midpoint between iliac crest and the costal margin of the lower rib.
- The patient should be asked to look straight ahead and to breathe out, at which point the measure should be taken.
- The measure should not be undertaken in pregnant patients, or patients with colostomies, ileostomies or ascites.

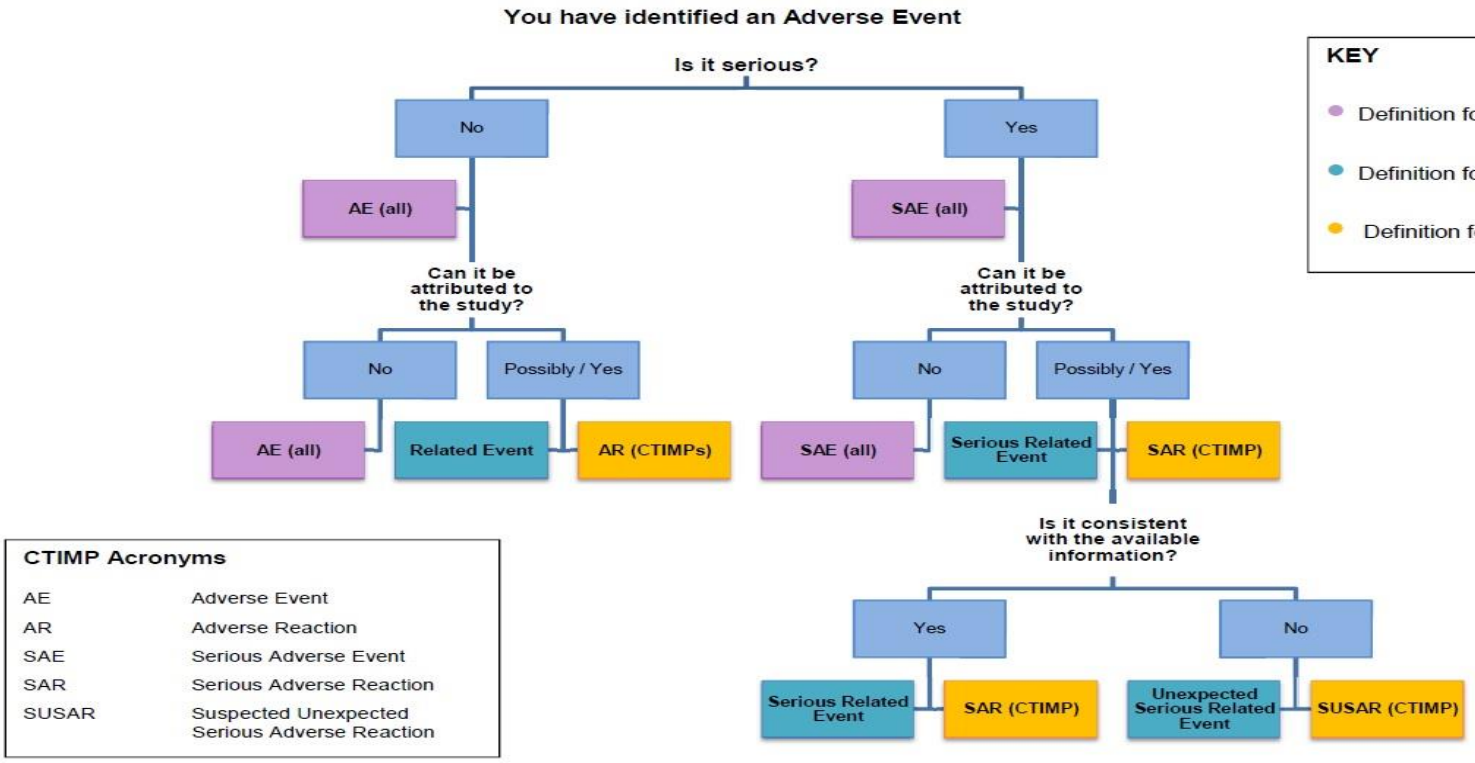
All measures should be interpreted according to the PENG pocket guide to clinical nutrition (Todorovic & Micklewright, 2011).

PROTOCOL APPENDIX 2: NIHR DECISION TREE FOR ADVERSE EVENT REPORTING

Introduction to Good Clinical Practice

NHS National Institute for Health Research Clinical Research Network

Decision Tree for Adverse Event Reporting



KEY

- Definition for CTIMPs and non-CTIMPs
- Definition for non-CTIMPs only
- Definition for CTIMPs only

CTIMP Acronyms

AE	Adverse Event
AR	Adverse Reaction
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
SUSAR	Suspected Unexpected Serious Adverse Reaction

1

PROTOCOL APPENDIX 3: EMBEDDED QUALITATIVE INFORMATION STUDY

Overview

A qualitative study will be embedded into KEATING, which will be referred to as the 'Information Study' in the patient information documents. The aim is to identify recruitment challenges and aid understanding of the patients' recruitment experience, by interviewing a sub-sample of patients and their relatives/ carers. Bespoke strategies will then be designed to optimise recruitment to future trials related to ketogenic diets and gliomas.

Recruiting patients to clinical trials is often a challenge. Patients' decision making processes are complex and can be influenced by various factors. Findings from qualitative studies embedded into clinical trials have identified how small changes in communication and trial protocol, along with a better understanding of patients' priorities at the point of approach, can help to facilitate recruitment (Hubbard et al., 2016; Poston et al., 2013; White and Hardy, 2010). Embedded designs are also beneficial for the development of bespoke implementation strategies. This approach of embedded qualitative interviews has demonstrated success at optimising recruitment in previous trials (Mills et al., (2003), Donovan et al., (2002), Avery et al., (2014)), and will ensure patients are supported in making an informed decision about KEATING.

The Information Study does not aim at identifying ways of somehow pursuing patients to participate in the trial, but rather to ensure patients are supported in making an informed decision and to improve their recruitment and trial experiences.

Sampling

A sub-sample of patients and their relatives/carers will be purposively selected for interview. Sampling for interviews will aim for maximum diversity and include those who consent to KEATING, those who do not consent for KEATING and those randomised to MKD and MCT KD. We understand that the principles of informed consent mean that when patients withdraw or decline trials they are not obliged to give a reason for their decision if they do not wish to. However, we will invite patients to participate in the Information Study even if they decline or withdraw from KEATING as they may wish to convey their perspectives and it is important to understand the experience of being approached about a clinical trial whatever decision a patient makes. We plan to sample both retrospectively and prospectively. Data will be collected until saturation is achieved; this is expected to be a maximum of 20 patient

interviews and 20 relative/ carer interviews (Harrop et al., 2016). Patients can be interviewed for their sole experience, whilst relatives will only be invited to participate as a dyad with the patient.

Methods

Prospective recruitment

All patients approached prospectively about the study will be approached for interview. After discussing the trial with the dietitian by telephone and receiving the KEATING patient information sheet, the patient will be routinely re-contacted and offered a screening appointment. If the patient declines participation in the main trial at that point, then the Information Study will be discussed with them in more detail. However, if a patient attends a screening appointment for the main trial, then the Information Study will be discussed with them at the end of that appointment.

If the patient expresses interest in participating in the Information Study, and would like a close relative or carer (person closely involved in their care) to consider participation, then the Information Study patient information sheet and relative/carer information sheet will be posted to the patient. The researcher will also discuss the study with the patient's relative/carer at this time, and seek their verbal consent to participate, if applicable. An appointment for interview will be scheduled at a time suitable for the participants, usually within four weeks of the last telephone conversation, allowing the participants adequate time to consider study involvement. The interview appointment can be cancelled by the participants at any time, without being obliged to give a reason for their decision. Consent will be sought from the patient and relative/carer immediately prior to the interview taking place.

Retrospective recruitment

Patients will also be recruited retrospectively, provided that they were approached about the study within three months of the date of ethical approval. We recognise patients can experience cognitive decline over the course of the disease. Therefore we consider this to be an appropriate time frame as these patients will still be receiving oncological treatment, thus the research team will be able to liaise with the clinical team to determine suitability (those patients experiencing cognitive decline will not be approached). The clinical team will initially discuss involvement in the Information Study with the patient and only if the patient agrees will they be formally contacted by a member of the research team.

The researcher will telephone those patients who agree to be contacted to discuss the Information Study. If the patient expresses interest in participating in the Information Study, and would also like a close relative or carer (person closely involved in their care) to consider participation, the researcher will also discuss the study with the patient's relative/carer at this time, and seek their verbal consent to participate (if applicable). The Information Study patient information sheet and relative/carer information sheet (if applicable) will be posted to the patient. An appointment for interview will be scheduled at a time suitable for the participants, usually within four weeks of the last telephone conversation, allowing the participants adequate time to consider study involvement. The interview appointment can be cancelled by the participants at any time, without being obliged to give a reason for their decision. Consent will be sought from the patient and relative/carer immediately prior to the interview taking place.

Interviews

Interviews will take place in the participants own home, workplace, by telephone or at WCFT depending on the participant's preference. Patient and relative/carer interviews will usually be undertaken separately, but can be undertaken jointly at the participant's request.

Topic guided, semi-structured qualitative interviews will explore participants experience and views of the recruitment process. Interviews will be conversational and participant centered. Questions will be open-ended and explore patients' and relatives' views and experiences of KEATING, the trial arms and the recruitment process. Interviewees will also be asked for their views on what might help to improve the recruitment process. Questions will be adapted as appropriate to whether patients consented or declined trial participation. All interviews will be conducted by the researcher (dietitian/PhD student) who has the necessary qualitative research skills. As the research as a dual role (dietitian and qualitative researcher), the interviews will be conducted in a gentle, sensitive and non-judging manner, to make the experience as comfortable as possible for participants. The topic guides have been designed to reflect this. Our focus is to explore the participants' views of KEATING, how it was discussed and the information they received. Any questions in which the participant feels obliged to justify their decision will be avoided. Participants will be free to decline to answer any questions or terminate the interview at any point. All interviews will be audio recorded and transferred onto a password protected file held on University of Liverpool Active DataStore.

Analysis of interviews

Audio recordings will be transcribed, checked and anonymised for analysis. Interview data will be analysed using a thematic approach (Braun and Clarke, 2006) for evidence of: i) the information communication needs of participants and relatives and ii) patients' and relatives' preferences and goals in relation to consent and recruitment. One member of the research team (KM) will lead a process of iterating between the developing analysis and new data, and other members of the qualitative study team (which will include at least one clinician) will develop and test the analysis by periodic discussion. Analysis will not take participants' accounts only at face value, rather our approach will be interpretive and consider both latent and manifest aspects of the data (e.g. what we can learn from the way that participants talk as well as the explicit content). The design, conduct and analysis of the qualitative study will be informed by procedures to support quality in qualitative research (Murphy et al., 1998, Seale 1999) including systematic data coding, triangulation and exceptional case analysis. Analysis will be assisted by qualitative analysis software.

Additional considerations

Participation in the qualitative study is voluntary, and patients will not be obliged to give a reason for non-participation in KEATING or the Information Study. Appointment letters sent to patients will be held within a password protected file, accessed only through a WCFT computer (see data protection, section 3.8.2). This will contain the patient's name, address and Walton ID number but not the relatives name and address. For interviews conducted by telephone, verbal consent will be obtained. If completed in person, written consent will be obtained (applicable to both patient and relative/carer interviews). Patients will be provided with a copy of their consent form, a copy will be held in the site file and the original in the medical notes. Relatives/carers will be provided with a copy of their consent form and the original will be held in the site file. The University of Liverpool Lone Working Policy will be followed by the research team when conducting interviews outside of the researchers' place of work.

The findings of the Information Study will be used to identify recruitment challenges and aid understanding of the patients' recruitment experience. This information will be used to design bespoke strategies to optimise recruitment to future trials related to ketogenic diets and gliomas. The findings will contribute to a PhD thesis, publications and presentations.

All recordings will be destroyed from the hand held device after analysis and stored and retained in keeping with data from the main trial, see sections 3.8.2 and 3.8.3. Transcripts

will also be stored and retained in keeping with data from the main trial, see sections 3.8.2 and 3.8.3.

APPENDIX J: PATIENT INFORMATION SHEET FOR KEATING TRIAL

APPENDIX K: DIETARY INFORMATION SHEETS FOR MCT KD AND MKD

APPENDIX L: EXAMPLE OF A SEVEN DAY MEAL PLAN

APPENDIX M: EXAMPLE FOOD DIARY

APPENDIX N: PATIENT INFORMATION SHEET FOR QUALITATIVE STUDY

APPENDIX P: NARRATIVE REVIEW METHODOLOGY AND SEARCH STRATEGY

Inclusion criteria

The initial inclusion criteria for the review are illustrated using the population, phenomena of interest and context (PICo) method in table P.1 (240).

Table P.1: A PICo table illustrating narrative review inclusion criteria.	
Population	People with advanced cancers.
Interest	People's views around decision making regarding participation in early phase clinical trials.
Context	Early phase clinical trials.

No restriction was placed on year of study or publication status. The search was limited to English language publications.

Search strategy

A three part search strategy was implemented to identify suitable studies for the review. This included electronic database searches, hand searching of included study references and other resources including conference posters and abstracts.

Electronic searches

The following electronic databases were searched.

8. Cochrane Library
9. CINAHL Plus
10. PsycINFO
11. ORRCA database
12. Google Scholar

The search was undertaken between 22nd and 26th June 2018. An example search strategy can be found in appendix Q. The search strategy and terms were adapted for use within other databases.

Hand searches

References from literature included in the review were hand searched to identify other possible studies.

Other resources

Conference abstracts and posters were included in the search to identify recent studies undertaken that may not yet be published or are ongoing.

Searches continued until a purposive sample was obtained, adopting the methods used in qualitative research, searching until a sufficient number of studies were retrieved to reach saturation (240). Wider articles were explored for context.

Screening included studies

All articles identified by the search were screening title and abstract. Those fitting the inclusion criteria were considered suitable for this narrative review (see P.2). An inclusive rather than exclusive approach was taken when obtaining full papers (240).

Table P.2: Eligibility criteria screening tool

	Inclusion	**Exclusion**
Population	☐ People with advanced cancers*	☐ People with other cancers
Interest	☐ Decision making regarding early phase clinical trials	☐ Other interests
Context	☐ Early phase clinical trials	☐ Non early phase clinical trials
Study design	☐ Any qualitative study	☐ All quantitative
Overall decision	☐ INCLUDED	☐ EXCLUDED
Notes		

Key: *Advanced cancers defined as cancers that cannot be cured or controlled, including metastasis.

APPENDIX Q: EXAMPLE SEARCH STRATEGY FOR NARRATIVE LITERATURE REVIEW

(Experience* OR perceive* OR perception* OR attitude* OR opinion* OR agree* OR accept* OR refuse* OR refusal OR decline* OR judge* OR prefer* OR consent* OR autonomy OR equipoise OR barrier* OR facilitate* OR opportunit* OR challenge*)

AND

(Qualitative OR "mixed method" OR feasibility)

AND

(Recruit* near/6 trial)

AND

(Cancer)

ORRCA database search strategy

ORRCA database recruitment domains: A5, B1, B3, B10, C3, D2

ORRCA database clinical area: oncology

APPENDIX R: QUALITATIVE INTERVIEW TOPIC GUIDES

(Version 3.0, 01/MAR/2018)

Topic guide for patient interviews for the qualitative study in KEATING

The aims of the study will be re-discussed with patients – We are interested in hearing about patient experiences of being approached to take part in the KEATING study. We understand that studies like KEATING can be a lot to understand and through this information study we are trying to learn how we can improve our explanations to patients and if we can make any changes to improve patient experience.

Reassurance will be provided regarding confidentiality and the interviewer will check the patient is happy to continue.

<u>Study information and recruitment process</u>

1. *I'd like to ask you some questions about the KEATING study…who initially told you about the study?*

Prompts: Can you tell me about the run up to the study? Can you remember when you were first diagnosed? Can you remember what was spoken about in terms of treatment options? Did they mention the study? Was this face to face or by phone? What information did they provide? When did they first discuss the study with you? Where were you up to with your treatment? Was this a good time to talk about studies? Where you expecting to be contacted by the dietitian? What were the main points that stood out from the conversation with the study team? What were your initial thoughts about the study? Is there anything would you change about how you were approached? When would you prefer to be approached? Who would you prefer to approach you about the study? Are there any improvements that could be made?

2. *What is your understanding of the reason why the study is being done?*

Prompts: What is your understanding of what the study aimed to investigate? What type of diet was it looking at and why? Are you able to tell me a bit about what this involves for patients? Did you have any prior knowledge of ketogenic diets in glioblastoma? Was anything unclear or confusing? What is your understanding of the risks and benefits are with this diet?

3. *We posted an information sheet to you about the study (demo). What are your views on it?*

Prompts: Did you find the wording and layout suitable? Is there anything that you would change? Were any parts helpful? Did you have any questions after reading the leaflet?

Decision making

4. *Before making your decision about taking part did you seek information from anywhere else?*

Prompt: Did you discuss your involvement in the study with your family or friends? Did you discuss the study with a doctor or nurse? Did either the doctors/ nurse or family/ friends provide you with opinions? How important were their opinions in your decision? Did you look into other sources of information, such as the internet – if so, then which sites/ organisations? Did you feel comfortable voicing your decision/ opinion? Would you have been as willing to take part withut your relative? How do you think that might have been?

5. *(Can you tell me about how you came to your decision to take part/not take part in the study?)*

Prompts: When did the decision start to form in your mind? How do you usually make decisions (gut reaction or evidence based/ informed decision)? How certain were you with your decision? How confident were you with your decision? How confident were you in telling others about your decision? Did you have an initial feeling about whether you wanted to take part or not? What are your thoughts on the use of ketogenic diets for people with glioblastomas? Did anything particularly worry you about the study? Did anything create a barrier to you participating? Did anything seem appealing about the study? Did you feel it was your decision? Were you given enough time to think things over? How do you feel about the information you were given to make the decision (more or less needed)? Do you have any particular views on being randomised to one diet or the other? Or the methods used to randomise?

6. *Are there any potential changes that could be made to alter your opinion?*

Prompts: Any changes to the study design? Changes to how you are told about the study and what it involves? How did you feel about the length of the study being 12 weeks?

7. *When thinking about the treatment you have received, is there any time when you think starting the diet would be most appropriate?*

Prompts: This could be not at all, before/after surgery, before/ during/ after radiotherapy or before/ during or after chemotherapy or after all treatment has finished. Can you tell me a bit more about that?

8. *Did you consider any other studies or treatments?*

Prompts: Other studies that may be open to you locally or nationally? Have you taken part in research previously? Would you take part in potential future studies? Have you looked into any other diets or nutritional supplements?

9. *If you had the chance to be involved in the study again would you make the same decision?*

Prompts: If changed decision why is that?

<u>KEATING participants only</u>

10. *What did you think when you were told about your allocated diet?*

Prompts: Did you have a diet preference? Did you have any worries or expectations? Do you have any particular views on being randomised to one diet or the other? Or the methods used to randomise. Would you rather have had a choice? Did your opinion influence how long you stayed on that diet?

11. *What has your experience of the KEATING study been so far?*

Prompts: Has your experience influenced your views on research? Do you have any tips for a similar study in the future? Has any part been particularly burdensome? Have there been times when the diet has been more difficult to follow? (E.g. fatigue). How did you feel around the time of finishing chemo/radiotherapy? How did this affect the diet? Has any part been particularly enjoyable? Have there been times when the diet has been easier to follow? Are there any motivating factors to staying on the diet? Are there any changes we could make to help people stay on the diet?

<u>Conclusion</u>

12. *Is there anything else you would like to talk about that we haven't covered? Do you have any questions for me? Thank you for taking the time to talk to me.*

General prompts:

Can you tell me more about that? What is your understanding of that?

Topic guide for relative interviews for the qualitative study in KEATING

The aims of the study will be re-discussed with the relative/carer – We are interested in hearing about relatives'/carers' experiences of the patient being approached to take part in the KEATING study. We understand that studies like KEATING can be a lot to understand and through this information study we are trying to learn how we can improve our explanations to patients and relatives/ carers and if we can make any changes to improve both of your experiences.

Reassurance will be provided regarding confidentiality and the interviewer will check the patient is happy to continue.

<u>Study information and recruitment process</u>

1. *I'd like to ask you some questions about the KEATING study….who initially told you about the study?*

Prompts: Can you tell me about the run up to the study? Can you remember when they were first diagnosed? Can you remember what was spoken about in terms of treatment options? Did they mention the study? Was this face to face or by phone? How did you feel about the patient being contacted? Did you speak to a member of the study team yourself? If so, what did they discuss with you? What were your initial thoughts? Is there anything you would change about the way you were both approached? Who would you prefer to be contacted by?

2. *What is your understanding of the reason why the study is being done?*

Prompts: What it is your understanding of what the study aims to investigate? What type of diet was it looking at and why? Are you able to tell me a bit about what it would involve for patients? Did you have any prior knowledge of ketogenic diets in glioblastoma? Was anything unclear or confusing? What do you think the risks and benefits are with this diet? How would it impact their lifestyle or routine?

3. *What would it involve for you as a relative/ carer?*

Prompt: Would it impact upon your lifestyle or routine?

4. *The patient received an information sheet about the study, did you read over it?*

Prompts: If so, what are your views on it? Did you find the wording and layout suitable? Is there anything that you would change? Were any parts helpful? Did you have any questions

after reading the leaflet? If you didn't read it, what are the reasons for this? Would you have liked to have read it?

Decision making

5. *Before the patient decided about taking part in the study, did they discuss the study and their involvement with you?*

Prompts: What were your thoughts about the study? What was your initial feeling about them taking part or not? When did the decision start to form in your mind? How do you usually make decisions (gut reaction or evidence based/ informed decision)? Did you seek information from elsewhere? Did you discuss the study with another family member or friend? Did you discuss it with their doctor or nurse? Did you consider other sources of information such as the internet? If so, which sites/ organisations? Do you feel your opinion influenced their decision to take part or not? Do you think they would have been as willing to take part without you? How might that have been?

6. *(How did you come to reach your opinion about their involvement in the study?)*

Prompts: How certain were you with your decision? How confident were you with your decision? What are your thoughts on the use of ketogenic diets for people with glioblastomas? Did anything particularly worry you about the study? Did anything create a barrier to the patient participating? Did anything seem appealing about the study? Were you both given enough time to think things over? How do you feel about the information you were given to make the decision (more or less needed)? Do you have any views on patients being randomised to one diet or the other? Or the methods used to randomise? Would you rather have a choice?

7. *Are there any potential changes that could be made to alter your opinion?*

Prompts: Any changes to the study design? Changes to how we tell patients about the study and what it involves? How we involve their relatives/carers in the process?

8. *Did you consider any other studies or treatments?*

Prompts: Other studies that may be open to you locally or nationally? Would you encourage the patient to take part in potential future studies? Have you looked into other diets or nutritional supplements?

9. *If the patient had the chance to be involved in the study again would your opinion of the study change?*

Prompts: If so, what are the reasons for this change of opinion? Do you think this would influence their decision to take part? If not, what has confirmed your opinion?

KEATING participants' relatives/ carers only

10. *What has your experience of the KEATING study been so far?*

Prompts: Has your experience influenced your views on research? Do you have any tips for a similar study in the future? Has any part been particularly burdensome? Have there been times when the diet has been more difficult to follow? (E.g. fatigue). How did they feel when they finished chemo/radiotherapy? Did this have any effects on the diet? How do you think they felt? Has any part been particularly enjoyable? Have there been times when the diet has been easier to follow? Are there any motivating factors to staying on the diet? Are there any changes we could make to help people stay on the diet?

Conclusion

11. *Is there anything else you would like to talk about that we haven't covered? Do you have any questions for me? Thank you for taking the time to talk to me.*

Topic guide for joint patient-relative interviews for the qualitative study in KEATING

The aims of the study will be re-discussed with patients and relatives/carers – We are interested in hearing about patient and relatives'/carers' experiences of being approached to take part in the KEATING study. We understand that studies like KEATING can be a lot to understand and through this information study we are trying to learn how we can improve our explanations to patients and relatives/carers, and if we can make any changes to improve both of your experiences.

Reassurance will be provided regarding confidentiality and the interviewer will check the participants are happy to continue.

<u>Study information and recruitment process</u>

1. *I'd like to ask you some questions about the KEATING study… who initially told you about the study?*

Prompts: Can you tell me about the run up to the study? Can you remember when you were first diagnosed? Can you remember what was spoken about in terms of treatment options? Did they mention the study? Was this face to face or by phone? Who initially told you about the study? Were you both present? What information did they provide? When did they first discuss the study with you? Where you expecting to be contacted by the dietitian? Did you both speak with the researcher by phone? How did you find the telephone discussion with the dietitian? What were the main points that stood out from the conversation with the dietitian? How did you both feel about being contacted? What were your initial thoughts about the study? Is there anything would you change about how you were approached? When would you prefer to be approached? Who would you prefer to approach you about the study? Are there any improvements that could be made?

2. *What is your understanding of the reason why the study is being done and what it involves for patients and for relatives?*

Prompts: What did it aim to investigate? What type of diet was it looking at and why? Are you able to tell me a bit about what the study would involve for patients? Are you able to tell me a bit about what the study would involve for relatives Did you have any prior knowledge of ketogenic diets in glioblastoma? Was anything unclear or confusing? What do you think the risks and benefits are with this diet? Would it impact upon your lifestyle or routine?

3. *We posted an information sheet to you about the study. What are your views on it?*

Prompts: Did you both read it over? Did you find the wording and layout suitable? Is there anything that you would change? Were any parts helpful? Did you have any questions after reading the leaflet?

Decision making

4. *Before making your decision about taking part did you seek information from anywhere else?*

Prompt: Did you discuss taking part in the study together? Did you discuss the study with a doctor or nurse? Did either the doctors/ nurse for family/ friends provide you with opinions? How important were their opinions in your decision? Did you look into other sources of information, such as the internet – which sites/ organisations? Do you think they would have been as willing to take part without you? How might that have been?

5. *Can you tell me about how you came to your decision to take part/not take part in the study?*

Prompts: When did the decision start to form in your minds? How do you usually make decisions (gut reaction or evidence based/ informed decision)? How certain were you with your decision? How confident were you with your decision? Did either of you have an initial feeling about whether you wanted (said patient) to take part or not? What are your thoughts on the use of ketogenic diets for people with glioblastomas? Did anything particularly worrying either of you about the study? Did anything create a barrier to you participating in the study or supporting (said patient) to participate in the study? Did anything seem appealing about the study to either of you? Did you feel it was the patient's decision or a decision you made together? Did you feel confident in voicing your opinion? Could anything be done to make you feel more confident in voicing your opinion? Were you both given enough time to think things over? How do you feel about the information you were given to make the decision (more or less needed)? Do you have any particular views about patients being randomised to one diet or the other? Or the methods used to randomise?

6. *Are there any potential changes that could be made to alter your opinion?*

Prompts: Any changes to the study design? Changes to how we tell you about the study and what it involves?

7. *When thinking about the treatment you have received, is there any time when you think starting the diet would be most appropriate?*

Prompts: This could be not at all, before/after surgery, before/ during/ after radiotherapy or before/ during or after chemotherapy or after all treatment has finished. Why is that?

8. *Did either of you look into any other studies or treatments?*

Prompts: Other studies that may be open locally or nationally? Have either of you taken part in research previously? Would either of you take part in potential future studies? Have you looked into other diets or nutritional supplements?

9. *If (said patient) had the chance to be involved in the study again would you both make the same decision?*

Prompts: If changed decision why is that?

<u>KEATING participants only</u>

10. *What did you think when you were told about your allocated diet?*

Prompts: Did either of you have a diet preference? Did either of you have any worries or expectations? Do you have any particular views on being randomised to one diet or the other? Or the methods used to randomise.

11. *What have your experiences of the KEATING study been so far?*

Prompts: Have your experiences influenced your views on research? Do either of you have any tips for a similar study in the future? Have there been times when the diet has been more difficult to follow? (E.g. fatigue). How did they feel when they finished chemo/radiotherapy? Did this have any effects on the diet? How do you think they felt? Has any part been particularly burdensome? Has any part been particularly enjoyable? Have there been times when the diet has been easier to follow? Are there any motivating factors to staying on the diet? Are there any changes we could make to help people stay on the diet?

<u>Conclusion</u>

Is there anything else either of you would like to talk about that we haven't covered? Do you have any questions for me? Thank you for taking the time to talk with me.

APPENDIX T: PUBLICATIONS DERIVED FROM THIS THESIS

Martin-McGill KJ, Tudur Smith C, Marson AG, Jenkinson MD. (2018). The modified ketogenic diet in adults with glioblastoma: an evaluation of feasibility and deliverability within the National Health Service. *Nutrition and Cancer*, *70*(4), doi: 10.1080/01635581.2018.1460677.

Martin-McGill KJ, Srikandarajah N, Tudur Smith C, Marson AG, Jenkinson MD. (2018). The role of ketogenic diets in the therapeutic management of adult and paediatric gliomas: A systematic review. *CNS Oncology, 7*(2), doi: 10.2217/cns-2017-0030.

Martin-McGill KJ, Tudur Smith C, Marson AG, Jenkinson MD. (2017). Ketogenic diets as an ajuvant therapy in glioblastoma (the KEATING trial): study protocol for a randomised pilot study. *Pilot and Feasibility Studies, 3*(67), doi: 10.1186/s40814-017-0209-9.