Interim guidelines for recurrent medulloblastoma
For children who received upfront craniospinal irradiation

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On behalf of the
Embryonal Brain Tumour Group

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Disclosure

This guideline only considers non-infant patients with recurrent medulloblastoma (> 3 years old at initial diagnosis) who received standard upfront therapy (maximal safe resection, craniospinal irradiation and chemotherapy) at diagnosis. It is now recognised that infant patients, specifically those with MB_{SHH} tumours/nodular desmoplastic histology are salvageable with CSI at disease recurrence [1]. This defined group of patients will be discussed separately in the CCLG Infant medulloblastoma guidelines.
Abbreviations

ANC     Absolute neutrophil count
cBNF    Children’s British National Formulary
CLA     Classic
CNS-PNET Central nervous system primitive neuro-ectodermal tumour
CSF     Cerebral spinal fluid
CSI     Craniospinal irradiation
DN      Desmoplastic nodular
EFS     Event free survival
FFPE    Formalin fixed, paraffin embedded
Gd      Gadolinium
GEMOX   Gemcitabine and oxaliplatin
GFR     Glomerular filtration rate
iFISH   Interphase fluorescent in situ hybridisation
IHC     Immunohistochemistry
IT      Intrathecal
LCA     Large cell anaplastic
MBEN    Medulloblastoma with extensive nodularity
MB\textsubscript{Group3} Medulloblastoma, Group 3 molecular subgroup
MB\textsubscript{Group4} Medulloblastoma, Group 4 molecular subgroup
MB\textsubscript{non-SHH} Medulloblastoma, non-Sonic Hedgehog molecular subgroup
MB\textsubscript{NOS} Medulloblastoma, not otherwise specified
MB\textsubscript{SHH} Medulloblastoma, Sonic Hedgehog molecular subgroup
MB\textsubscript{WNT} Medulloblastoma, WNT molecular subgroup
MEMMAT Metronomic and Targeted Anti-angiogenesis Therapy for Children with Recurrent/Progressive Medulloblastoma
MTD     Maximum tolerated dose
NOS     Not otherwise specified
OS      Overall survival
PFS     Progression free survival
SMO     Smoothened
<table>
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<tr>
<td>TEMIRI</td>
<td>Temozolomide and irinotecan</td>
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<td>VP</td>
<td>Ventriculoperitoneal</td>
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<td>WBC</td>
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Introduction

Background
Patients who relapse with medulloblastoma following standard upfront therapy have a poor outlook with an overall survival rate of approximately 5% [2-8]. Management of these patients remains a considerable clinical challenge and there is currently no consensus on life-prolonging treatment [2]. Furthermore, there remains a lack of clarity with regards to which group of patients may benefit from salvage treatment with curative intent [9]. Factors believed to be important in selecting patients that may have curable disease at relapse are; local recurrence, minimal residual disease at the point of proceeding to a high-dose procedure, chemotherapy responsiveness to initial cytoreductive therapy and the ability to deliver radiotherapy at relapse in patients who received minimal treatment upfront (e.g. infant patients who did not received craniospinal irradiation (CSI)). However, many of the studies of relapsed disease are small, and do not have the overlay of contemporary molecular biology now understood in the disease at diagnosis [5, 10-17].

In the last decade, a huge amount of progress has been made in our understanding of the molecular biology of medulloblastoma at diagnosis. For example, following a consensus meeting in 2012, it was agreed that medulloblastoma consists of 4 molecular subgroups (MBWNT, MBShh, MBGroup3 and MBGroup4) [13, 14]. However, these subgroups and their interplay with clinicopathological and additional molecular features are currently under revision. Whilst the overarching 4 subgroups remain there is further refinement within these groups, which are biologically and clinically relevant, adding to upfront disease risk stratification [15-17]. Despite these advances in the understanding of the biology of medulloblastoma at diagnosis, only a small number of studies have been undertaken in the disease at relapse [18-21]. The reasons for the paucity of studies is likely to be multifactorial; medulloblastoma recurrence is a rare event, there have been few clinical trials and, as a likely consequence of the poor prognosis and lack of clinical studies, biopsy has not been routinely performed. Evidence is emerging, however, that the biology of disease both at diagnosis and relapse can influence disease progression, timings and patterns of relapse [19, 22]. It is anticipated that as our understanding of disease biology at recurrence increases, further factors will influence treatment decisions at relapse [18, 19].

Biology of relapsed medulloblastoma
Two independent studies have demonstrated that the 4 major molecular subgroups; MBWNT, MBShh, MBGroup3 and MBGroup4, remain stable over time i.e. tumours sampled from the same patient do not change molecular subgroup between diagnosis and relapse [18, 19]. However, when clinicopathological and additional molecular features are contrasted between diagnosis and relapse biopsies sampled from the same patient, there are clear differences. Acquisition of high-risk features such as metastatic disease, large-cell anaplastic (LCA) histology, MYC oncogene family amplification and p53 pathway defects are frequently observed at disease recurrence [18, 20]. Furthermore, Hill et al. demonstrated that the biology of the tumour at relapse determined disease behaviour post-relapse. The combination of p53 pathway defects and acquired MYC oncogene amplification, observed in 7/22 (32%) tumours at relapse predicted a rapid decline post-recurrence with all patients dying within 9 months [18]. Combined P53-MYC defects is the first biomarker to be
discovered in the disease at relapse, but requires independent, prospective validation. However, additional studies also highlight that the biology of the disease at relapse differs significantly from the disease at diagnosis, with often a greater burden of aberrations observed at recurrence [18, 20, 21].

MB_{WNT} tumours have a good prognosis and therefore relapsed disease, following standard upfront treatment, consists predominantly of MB_{SHH}, MB_{Group3} and MB_{Group4} tumours [13, 19, 23, 24]. Upon establishment of subgroup stability between diagnosis and relapse, inferences can be made from the molecular subgroup determined at diagnosis, and the patterns, timings and outcomes of relapsed disease between molecular subgroups. Early reports suggest that MB_{Group4} are more likely to relapse late, with a significant proportion recurring beyond 5 years post-diagnosis [19, 22, 25]. Additionally, both MB_{Group3} and MB_{Group4} tend to recur at distant sites [19, 25]. Other studies suggest that patients with local relapses have a prolonged median survival [26]. However whilst these observations are helpful for prognostication and guiding disease monitoring, there are no agreed features that can identify the 5% of patients who might survive their disease recurrence.
Review of treatment strategies at medulloblastoma recurrence

High-dose chemotherapy
In 1996 and 1998, Finlay et al. and Gururngan et al. both reported on a subset of patients with relapsed brain tumours who were salvageable with high-dose chemotherapy and autologous stem cell rescue [27, 28]. Overall survival (OS) rates reported by Gururngan et al. were 50% with a median follow-up of 37.9 months post-stem cell transplant [28]. A follow-on study in relapsed medulloblastoma only reported on 23 patients, 16 previously treated with upfront radiotherapy, who received high-dose thiotepa, etoposide and carboplatin in the setting of minimal residual disease. Toxicity was substantial, however the EFS rate was 30% with a median follow-up of 54 months post-stem cell transplant [29]. More recently, retrospective studies evaluating the utility of a variety of high-dose procedures (thiotepa, etoposide, carboplatin, cyclophosphamide, melphalan, busulfan and topotecan) for relapsed medulloblastoma report contrasting survival rates ranging from 0-51%. The majority of these regimens report significant toxicities and are difficult to interpret because of selection bias, confounding factors, small numbers, and single institutional experiences [6, 9, 12, 30, 31]. In an effort to consolidate these findings a consensus workshop in 2006 evaluated 8 studies totalling 231 patients with recurrent medulloblastoma, (202 treated with upfront radiotherapy), who were treated with high-dose chemotherapy at relapse. In total 159 patients received high-dose chemotherapy, 133/159 had received prior upfront radiotherapy and 23/133 (17.3%) were long term survivors at the time of reporting. However, when considering the 2 national prospective studies (HIT-REZ 967 and UKCCSG) that reported survival from the point of relapse on all patients, and delivered high-dose chemotherapy with curative intent, the combined OS was only 4.2% [5, 26, 32].

HITREZ 97 multicentre trial (1997-2003)
This trial encompassed patients aged 0-30 years with progressive or relapsed primitive neuroectodermal tumours (medulloblastoma, supratentorial PNET and pineoblastoma). There were 2 treatment arms; oral chemotherapy or high-dose chemotherapy which comprised of 96 hours continuous infusions of carboplatin and etoposide to assess chemosensitivity, followed by high-dose carboplatin, etoposide and thiotepa in good responders. Seventy-two patients (63 with medulloblastoma) were selected to receive high-dose chemotherapy, based on clinician, patient or family preference. Sixty-three (88%) of these patients had received prior radiotherapy at initial diagnosis. Thirty-four of the total 72 patients (48%) were good responders, and 24 proceeded to high-dose chemotherapy, a further 3 patients with stable disease also continued to high-dose chemotherapy (n=27). Median PFS and OS for the 27 patients were 8.4 and 20.2 months respectively. There was no significant difference in PFS or OS between the good responders who did or did not receive high-dose chemotherapy. Toxicity was severe with an 8% treatment related mortality and grade III- IV mucosal, haematological, infectious and hearing toxicities frequently observed. Ultimately only 2 of the 72 patients (2.7%) originally selected for high-dose chemotherapy were reported to be in continuous remission [26].

UKCCSG Recurrent PNET (CNS 2000 01) trial (2000-2007)
This observational study recruited 40 patients aged<21 years with recurrent medulloblastoma and 5 with relapsed CNS-PNETs. All patients with the exception of 1 had
received upfront CSI. At relapse all patients received cytoreductive therapy with cyclophosphamide and local therapy where appropriate. Only 22 patients received cycle 1 of high-dose chemotherapy (thiotepa) and of these, 12 received cycle 2 of high-dose chemotherapy (carboplatin). Toxicities included hyperpigmentation, haematuria and grade III ototoxicity. At the time of reporting 3 patients were alive, all of whom had initial isolated solitary relapses (1 posterior fossa, 2 metastatic) and re-resection, 1 of whom had subsequently relapsed for the second time. Thirty-five patients died of tumour progression, 1 of respiratory failure and 1 of post-treatment myelodysplasia. Overall, the median EFS and OS was 1.0 year and 1.6 years and 5 year EFS and OS was 8.7% and 8.2% respectively [32].

**Standard chemotherapy**

**TEMIRI (2007-2010)**
The utility of irinotecan in refractory/relapsed medulloblastoma in combination with temozolomide, was investigated in a phase II, multicentre ITCC and SIOPE study. Sixty-six patients were recruited, 59 of whom had received previous CSI. Overall only 48 patients were considered to have evaluable disease; 18 patients had incomplete assessments or poor image quality. The objective response rate was 33% during the first 4 cycles and the estimated probability of remaining disease free at 6 months was ~45%. Toxicities included; gastrointestinal disturbance, myelosuppression, electrolyte disturbances and liver function test abnormalities. Five patients had prolonged responses ranging from 30-75 weeks attributable to TEMIRI [33]. Furthermore a recent review of early phase trials in recurrent medulloblastoma (page 16) highlighted that overall TEMIRI produces the best objective responses rates and diseases control rates, albeit with short follow-up, when evaluating the 4 available medulloblastoma/CNS-PNET specific early phase trials. The remaining 3 trials were investigating vismodegib, temozolomide, and etoposide [34-37].

**Metronomic chemotherapy**

Metronomic chemotherapy, defined as the chronic administration of chemotherapeutic agents without prolonged drug-free breaks, at low, minimally toxic doses, is believed to work by inhibiting tumour growth through anti-angiogenic mechanisms, promoting apoptosis and immune-surveillance [38-40]. Metronomic therapy use is now commonplace in a variety of relapsed scenarios; local relapse, leptomeningeal recurrence and multiple prior therapies. Low-dose repeated cycles of oral etoposide has been used in disease recurrence for decades. Bone marrow suppression is the typical major toxicity reported, non-haematological toxicities include mucositis, nausea/vomiting, diarrhoea, alopecia. However treatment is normally well tolerated and non-sustained partial responses are frequently observed [41-44]. Reports also support the use of temozolomide at recurrence with complete and partial responses noted. Similarly myelosupression is the most frequently observed side-effect. Non-haematological toxicities include; abdominal pain, nausea, vomiting, constipation, liver function test abnormalities and anorexia. Differing temozolomide dosing regimens have been utilised with similar toxicities and responses observed [45-50].

Combinations of metronomic therapy have also been tested in recurrent medulloblastoma. A phase I trial designed to established the maximum tolerated dose (MTD) of oral etoposide
and temozolomide, in relapsed/refractory medulloblastoma (n=14) demonstrated good
tolerance and tumour response. Similar toxicities to single agent delivery were reported
including myelosuppression and transaminitis [35]. Peyrl et al. reported on 16 patients with
recurrent embryonal brain tumours treated with bevacizumab, thalidomide, celecoxib,
fenofibrate, etoposide, cyclophosphamide and intrathecal therapy (alternating liposomal
cytarabine and etoposide). Seven patients with recurrent medulloblastoma were treated.
At 6 months, OS and EFS was 100% for all 7 patients, 85.7% at 12 months and 68.6% after 24
months. Toxicities included; grade III-IV neutropenia, grade III infection, peripheral
neuropathy (secondary to thalidomide), hypothyroidism, proteinuria and haematuria.
Papilloedema and raised intracranial pressure were noted following intraventricular
liposomal cytarabine in 2 patients. Secondary leukaemias have also been reported following
prolonged exposure to metronomic therapy [38, 40]. As a result of this promising report a
phase II study has commenced; Metronomic and Targeted Anti-angiogenesis Therapy for
Children with Recurrent/Progressive Medulloblastoma (MEMMAT, NCT01356290).

MEMMAT update (2014-2022)
Prior to trial commencement 15 patients, diagnosed between 2006 and 2013 with a
recurrent medulloblastoma, were treated across 2 institutions with bevacizumab,
thalidomide, celecoxib, fenofibrate, etoposide alternating with cyclophosphamide and
intrathecal therapy (IT) (liposomal cytarabine and etoposide). At the time of reporting 8
patients demonstrated complete responses with 10/15 still alive (follow-up; 3-66 months).
Four patients died of tumour progression and 1 died of other, unrelated, causes. Overall
survival was 84.4% at 1 year and 65.7% at 5 years, EFS was 77% and 44% at 1 and 5 years
respectively [51].

Currently the MEMMAT trial is still recruiting and liposomal cytarabine (DepoCyte) has been
withdrawn from the market, therefore complete data is not available for this guideline.
However there are now 20 patients who have received chemotherapy, as per the MEMMAT
trial, who are not on study. Seventeen of these 20 patients received prior CSI, and alongside
metronomic therapy 13/20 have received additional therapy at disease recurrence (e.g.
high-dose chemotherapy, reirradiation etc.). Overall 17/20 displayed metastatic disease
and 18/20 received IT therapy. At the time of correspondence, 4/20 patients were in
continuous remission, 4 in remission following re-starting therapy and 6 patients were
disease free and off treatment. Overall survival and PFS at 5 years were 62% and 24%
respectively (I Slavc, Medical University of Vienna, Austria, personal correspondence).

Despite these promising results, caution should be applied when interpreting preliminary
data. We therefore await the final results of the MEMMAT trial before considering a
recommendation for the regimen at medulloblastoma recurrence.

Targeted therapies
SHH pathway inhibitors
Gajjar et al. reported on a dose finding study of vismodegib, a smoothened (SMO) inhibitor,
in 33 patients [37]. Five experienced progressive disease during the first course and 1
patient withdrew from the study. Acute dose-limiting toxicities included; electrolyte
imbalances, myelosuppression and abnormal liver function tests. Long-term toxicities are
known to include; teratogenic potential, bone and teeth growth defects. Serial MRIs
conducted during the study identified new bony changes such as; cartilaginous clefts, bone bridges and increasing focal femoral physeal thickening. The subsequent phase II study, reported on 12 paediatric patients with relapsed/refractory MB_{SHH} tumours. Here they reported a low toxicity profile, 1 sustained response in a MB_{SHH} tumour but no significant difference between the PFS of the MB_{SHH} tumours and the MB_{non-SHH} tumours (n=13) in the paediatric cohort. In the adult cohort, patients with MB_{SHH} tumours did have a significant response when compared to MB_{non-SHH}. They also reported on potential mechanisms of primary resistance, a phenomenon now recognised in the disease, with response to SMO inhibition dependent on the level of pathway disruption in the MB_{SHH} tumour [36, 52].

Two recent reports have identified irreversible growth plate fusions in children treated with either vismodegib or sonidegib. The first report described 3 patients, treated with prolonged (>140 days) vismodegib who developed widespread growth plate fusions. All 3 patients now have disproportionate growth, profound short stature, and interestingly 2 of the 3 patients subsequently developed precocious puberty; a finding which requires further exploration. Similarly in the recently published phase I/II trial of sonidegib, which included 60 paediatric patients (39 with relapsed medulloblastoma), 3 patients demonstrated evidence of growth plate closure [53]. Currently, the use of vismodegib at diagnosis is restricted to skeletally mature patients. The use of SHH inhibition in incurable recurrent/refractory medulloblastoma is complex with some responses demonstrated in MB_{SHH} but often not sustained [52, 54].

**Intrathecal chemotherapy**

Meningeal dissemination represents the rationale for using IT therapy to overcome the blood brain barrier. The half-life of IT chemotherapy is typically short, but the use of liposomal cytarabine enables the slower release into the CSF. Furthermore there is evidence of more rapid elimination of liposomal cytarabine after lumbar administration when compared to ventricular administration. Several small studies report on the use of liposomal cytarabine in relapsed medulloblastoma, both in isolation and in combination with other therapies. Side effects included chemical arachnoiditis, lethargy, ataxia, back pain, nausea, vomiting, headache and slurred speech and current recommendations for its use is with caution and only with concomitant dexamethasone to prevent arachnoiditis. CSF clearance of disease following IT liposomal cytarabine is reported but the additional benefit is difficult to evaluate given small study numbers and the frequent use of adjuvant chemotherapy [8, 55-59]. Furthermore, liposomal cytarabine has recently been withdrawn from the market due to manufacturing issues, and therefore its ongoing use in relapsed medulloblastoma is not feasible.

Other agents have also been trialled in relapsed/refractory medulloblastoma such as etoposide and mafosfamide [60-62]. Again these studies report clearance of CSF disease in some patients but were either phase I, combined with other tumour types, or/and in combination with other treatments so assessing the role of IT therapy on extending survival remains difficult. Furthermore potential acute toxicities attributable to IT etoposide were reported in 28% of the HIT REZ 97 study and included; seizures, headaches, isolated fevers, nausea, vomiting and fatigue. Potential long-term side effects included; dysarthria, ataxia, impaired concentration, secondary malignancy and memory disturbance [60].
Reirradiation

Reirradiation is increasingly considered in the era of advancing radiation techniques for tumours such as ependymoma although it is not without risk of serious toxicity [63-66]. In medulloblastoma Dunkel et al. reported on the long-term outcomes of a prospective single-arm study from 1990-1999 undertaken on 25 patients with disease progression or evidence of first relapse. All patients had undergone upfront resection and CSI with or without adjuvant chemotherapy at initial diagnosis. At recurrence all patients received high-dose chemotherapy as per CCG-9883 (carboplatin, thiotepa and etoposide) with autologous stem cell support [3, 29]. Five patients received further external beam irradiation (3 focal, 2 CSI) delivered either pre or post high-dose chemotherapy. Overall, 3/25 patients had early treatment related deaths and toxicity was substantial in all remaining patients. Overall 16/22 patients progressed with a median survival after recurrence of 12.3 months. Six long-term survivors were reported generating an EFS and OS at 10 years of 24%. There was a trend towards improved survival in patients who received radiotherapy (p=0.07) as part of their salvage therapy but specific toxicities in these patients were not reported.

A cohort study, undertaken by Miker-Zabel et al. reviewed the survival and side effects of stereotactically-guided radiotherapy in 20 patients with recurrent medulloblastoma, who all received upfront CSI. Twenty-nine lesions received treatment, 21 fractionated stereotactically-guided radiotherapy and 8 radiosurgery. Survival following re-irradiation at relapse was reported as 65% at 1 year, 25% at 3 years and 17% at 5 years. No acute or chronic grade III or above toxicities, secondary malignancies or symptomatic radionecrosis were reported [67]. Similarly Saran et al. reported retrospectively on 12 heavily pre-treated (CSI +/- chemotherapy) patients who underwent treatment with hypofractionated stereotactic conformal radiotherapy (SCRT) for their recurrent medulloblastoma tumours. Treatment was generally well tolerated, with reports of acute raised intracranial pressure post-treatment and radiation necrosis as a long-term toxicity (n=1). Here they demonstrated a high-local control rate at 1 year (80% PFS), however overall long-term disease control was rare, with metastatic recurrence/progression dominating [68].

Massimino et al. reported on the utility of high-dose chemotherapy with or without re-irradiation [4]. Seventeen patients were treated, 16 previously treated with CSI. Either 1 or 2 cycles of high-dose thiotepa (+/- carboplatin) were administered to all responders (n=15) following induction chemotherapy. Ten patients received reirradiation (7 CSI, 3 focal). Three-year EFS and OS rates were 19% and 56% respectively. Thirteen of the 15 patients that completed all planned treatment, relapsed with disease. One patient died of other causes and only one patient was reported to be in a continued remission beyond 93 months (localised spinal relapse completely excised). Here, again, they concluded that high-dose chemotherapy, even with the addition of re-irradiation was not a curative strategy in recurrence following standard upfront therapy [4].

A single centre study undertaken at Memorial Sloan-Kettering Cancer Centre, retrospectively reviewed all patients who received external beam reirradiation as part of their salvage treatment (1992-2009, n=13). Treatment at diagnosis for all patients included upfront CSI. Reirradiation at relapse reflected the era of treatment and pattern of recurrence and median cumulative dose was 84Gy. Eleven patients completed their
planned reirradiation course, 6/11 progressed, 3 within field (median 17 months, range 2-59 months following completion of reirradiation). Of the 2 patients that did not complete their planned reirradiation, 1 progressed, 1 continued with chemotherapy with visible disease present. EFS and OS at 5 years for the entire cohort from time of first recurrence was 48% and 65% respectively. Interestingly 83% of patients who had no visible disease on entering reirradiation treatment, displayed a continued remission (median follow-up 92 months). No treatment related deaths, acute toxicities as a result of reirradiation or secondary malignancies were reported. One case of asymptomatic radionecrosis was observed [69].

Finally more recently a retrospective review of 38 patients initially treated with similar standard upfront therapy according to SJMB96 protocol (ClinicalTrials.gov:NCT00003211) or SJMB03 (ClinicalTrials.gov:NCT00085202) was undertaken to evaluate the survival benefit of reirradiation in relapsed medulloblastoma. Fourteen patients received reirradiation (8 CSI, 6 focal) following chemotherapy and/or surgery. Selection for reirradiation was based on clinical scenario and patient/family preference. Patients with a higher burden of disease were typically not selected for reirradiation. Median and cumulative maximal doses of the reirradiation course were 30Gy and 84Gy, respectively. Comparing patients with standard risk disease at initial diagnosis (n=17), 10 year OS from initial diagnosis was 45% for the reirradiated population versus 0% in patients who did not receive reirradiation (p=0.036). Similar results were observed for patients with initial high-risk disease (n=21, p=0.003). At the time of reporting 6 out of the 11 standard-risk reirradiated patients had progressed (5 outside the boost area but within the CSI field, 1 both inside and outside the boost area). Five standard-risk patients remain alive with no evidence of disease but follow-up is still relatively short. Of the 3 high-risk patients who received re-irradiation (all focal), 2 have subsequently progressed [2].

Review of early phase trials in relapsed and refractory medulloblastoma
A recent systematic review of phase I/II clinical trials over the last 15 years, encompassing patients less than 18 years old with refractory/relapsed medulloblastoma identified a total of 566 patients in 78 studies that met inclusion criteria [34]. Several studies included CNS-PNETs therefore 662 patients were available for combined evaluation. Half of the studies evaluated conventional chemotherapies, and 35% targeted agents. Several key points were highlighted;

- Median objective response rate for all patients with medulloblastoma (n = 662) was 0% (range 0–100).
- Median objective response rate in phase I studies was 0% (range 0–100) and 6.5% (range 0–50) in phase II studies.
- Median disease control rate in phase I studies was 16% (range 0–100) and 25% (range 0–75) in phase II.
- Platinum agents showed a median objective response rate from: 0 to 7% (single agent); combined with etoposide, 33%; combined with irinotecan, 100% (n=2 patients with medulloblastoma) [70].
- Temozolomide overall demonstrated a median objective response rate of 16.5% and disease control rate of 36.5%. Examining phase II studies containing temozolomide, there was a median objective response rate of 33% and a median disease control rate of 57%. 
• In the phase II study of temozolomide and irinotecan, overall response rates were 33% and disease control rates were 73% [33].

• Smoothened inhibitors produced objective response rates of 6% (sonidegib) and 3% (vismodegib). All of these studies however had limitations, such as the inclusion of MB_{non-SHH} tumours in their analysis.

• Antiangiogenic therapy containing regimens varied but produced objective responses ranging from 0-100%. However, the 100% objective response rate refers to one patient with a medulloblastoma who responded to a combination of bevacizumab, vincristine, irinotecan, and temozolomide (VITb) and was therefore consolidated with radiotherapy [71].

Whilst this review has its limitations, they concluded that temozolomide has the most promising activity as monotherapy and in combination with irinotecan for relapsed/refractory medulloblastoma [33, 50].

Survey of practice in the UK
A recent case based nationwide survey of practice conducted between 2016-2017, highlighted the variation of practice across the UK for the treatment of relapsed medulloblastoma and emphasised the need for clearer guidance. Similar themes of suggested treatment for the five cases studies circulated did emerge however, with oral temozolomide, oral etoposide, MEMMAT therapy and early phase studies as the most frequent suggestions. On further individual enquiry, focussed on whether centres were achieving MEMMAT therapy only 3 centres had delivered all agents included in the MEMMAT protocol to 3 individuals [51].

Personal correspondence
To aide in the compilation of this review and guidelines, international colleagues were contacted to share their experiences. Many thanks to M Massimino (Istituto Tumori, Milan, Italy), E Bouffet (The Hospital for Sick Children, Toronto, Canada), V Ramaswamy (The Hospital for Sick Children, Toronto, Canada) and A Gajjar (St. Jude Children’s Research Hospital, Memphis, USA) for contributing to the discussion. A variety of regimens were adopted but similar themes were witnessed throughout. For example, in isolated lesions surgery and reirradiation would be considered. Again the favoured/suggested agents and regimens included oral temozolomide, oral etoposide and TEMIRI. Other regimens discussed included; metronomic therapy, gemcitabine and oxaliplatin (GEMOX), temozolomide, irinotecan and bevacizumab, (Children’s Oncology Group phase II study ACNS0821) and high-dose procedures for selected patients (i.e. MB_{Group4} if they are chemo-responsive, [72-74]).
Rationale for treatment recommendations

Whilst the prognosis for most patients with a relapsed medulloblastoma is poor there is a consistent, small proportion of patients who may be long-term survivors (~5%). At present the clinicopathological and molecular features to assist in identifying these potential survivors are not established. However patients with solitary, isolated relapses which are amenable to surgical resection have been shown to have a prolonged survival in the most recent medulloblastoma study (HIT-SIOP-PNET4) undertaken in Europe [75]. Current practice therefore considers these patients to have a small, albeit unlikely, chance of cure, and therefore local therapy options including surgery and radiotherapy should be considered in conjunction with the below chemotherapy recommendations.

In summary the treatment recommendations, based on consideration of the presented evidence alongside current acceptable practice both nationally and internationally are as follows:

Neurosurgery and radiotherapy

- Neurosurgical resection in isolated lesions (complete or near complete) or for symptom relief (debulking).
- Biopsy should be considered and discussed where appropriate if resection is not appropriate.
- Biopsied and resected samples should be prioritised for confirmation of clinical diagnosis including molecular characterisation (Appendix B), submitted to the CCLG tumour bank, and where possible entered onto the paired relapsed medulloblastoma research study (page 19).
- Reirradiation should be considered on an individual patient basis, particularly in isolated lesions. It is beyond the remit of these guidelines to recommend radiotherapy guidance.

Chemotherapy

The different chemotherapy regimens are recommended to be tailored to individual patients, family and patients’ wishes and clinician discretion. The use of intensive high-dose chemotherapy regimens are not recommend for patients with relapsed medulloblastoma who received standard upfront therapy including CSI. The chemotherapy regimens advised below are not exclusive and more than one regimen can be utilised for an individual.

Where a localised recurrence has been excised and/or irradiated it is recommended that chemotherapy, as outlined below, should be considered to consolidate local therapy. Please contact the authors of this guideline for further advice (page 5).

- Early phase trial entry where appropriate.
- Oral temozolomide.
- Oral etoposide.
- Oral temozolomide with irinotecan (TEMIRI).
General therapy guidance

**Recommended investigations**

- MRI brain and spine pre-operatively (as per CCLG radiology guidelines, Appendix A).
- Surgical resection is strongly encouraged to:
  - confirm diagnosis,
  - for total or near-total resection in isolated nodular recurrences,
  - debulk tumour for symptomatic relief.
- Consent for CCLG tumour banking.
- Post-op MRI within 48 hours of surgery in tumours where total or near-total resection is undertaken.
- Histology and molecular risk stratification (Appendix B).
- Lumbar puncture examination of CSF, ≥ 10 days post-surgery is recommended to complete staging when near-total/total resection is undertaken in isolated lesions.

**This guideline encompasses treatment for:**

- MRI and/or biopsy confirmed relapsed medulloblastoma.
- Patients ≥ 3 years of age who have received previous craniospinal irradiation.
- Histology: classic (CLA), desmoplastic nodular (DN), medulloblastoma with extensive nodularity (MBEN), large-cell/anaplastic (LCA) or histology not otherwise specified (NOS).
- All molecular subgroups (MB_WNT, MB_SHH, MB_Group3, MB_Group4 or MB_NOS).

**Molecular assessments offered by the National Reference Service**

- Histopathological review, immunophenotype and molecular subgroup (to include; H&E, reticulin, GFAP, synaptophysin, neurofilament, p53, INI-1 (BAF47), beta-catenin, EMA, Lin28, Ki-67 (MIB-1), p75-NGFR (or GAB1), OTX2 and YAP1 immunostains).
- Medulloblastoma molecular subgroup status by a second method (850K DNA methylation array or MassArray).
- Mutational status of CTNNB1 and TP53.
- Copy number status of MYC, MYCN and chromosome 6 (by FISH or SNP array).
- For further information see Appendix B.

**Relapsed medulloblastoma study**

There is currently a recruiting research study for relapsed medulloblastoma [18]. If a biopsy at recurrence is taken, consent for the CCLG Tumour Bank is strongly recommended. Freshly frozen tissue is preferred for this study but formalin fixed, paraffin embedded (FFPE) material will also be accepted. Please contact the below team to alert them to the possibility of a research sample.

- Dr Rebecca Hill: [Rebecca.Hill@newcastle.ac.uk](mailto:Rebecca.Hill@newcastle.ac.uk) or [Rebecca.Hill@nuth.nhs.uk](mailto:Rebecca.Hill@nuth.nhs.uk)
- Prof Steve Clifford: [Steve.Clifford@ncl.ac.uk](mailto:Steve.Clifford@ncl.ac.uk)
- Dr Stephen Crosier: [Stephen.Crosier@newcastle.ac.uk](mailto:Stephen.Crosier@newcastle.ac.uk) or [S.Crosier@nhs.net](mailto:S.Crosier@nhs.net)
Summary of treatment recommendations

Confirmation of diagnosis

- MRI imaging only
  - Consider biopsy
- Biopsy and MRI imaging

Consent for CCLG Tumour Bank
Contact Relapsed Medulloblastoma Study Team

Complete staging
- MRI head and spine with contrast
- Lumber puncture ≥ 10 days post-surgery (when near-total/total resection is undertaken in isolated lesions)

- Isolated lesion completely or nearly completely excised (<1.5cm² residual)
  - Consider reirradiation
    - Discuss with Embryonal Brain Tumour Group
  - Consider chemotherapy
    - Discuss with Embryonal Brain Tumour Group

- Metastatic disease or unresectable/not resected isolated lesion

Recommended chemotherapy regimens*
- Early phase trial entry where appropriate
- Oral Temozolomide
- Oral Etoposide
- Oral Temozolomide with Irinotecan (TEMIRI)

*The chemotherapy regimens advised are not exclusive and more than one regimen can be utilised for an individual.
**Oral temozolomide** [45, 46, 49, 50]

**Baseline evaluation**
Baseline evaluation includes a complete medical history, general and neurological examination, and haematological and biochemical assessments. Medical and neurological examinations are performed prior to each cycle.

**Starting criteria for each cycle**
- Cycle 1: satisfactory recovery from all previous therapies, with ideally **4 weeks** since the last dose of previous chemotherapy and/or radiotherapy.
- Absolute neutrophil count (ANC) ≥1×10^9/L.
- Platelet count ≥100×10^9/L (transfusion independent).
- Haemoglobin level ≥80 g/L.
- Serum creatinine ≤1.5 ULN.
- AST or ALT ≤2.5 ULN and total bilirubin ≤1.5 ULN (except in Gilbert’s syndrome).

FBC and biochemical profile should be monitored every **2 weeks** and tailored to the individual once a stable dosing regimen has been achieved. If the starting criteria are not met, treatment can commence at the discretion of the treating clinician.

**Cycle 1 (28 days)**
- Temozolomide 150mg/m^2, once a day, orally, day 1-5.

**Cycle 2 onwards (28 days)**
- Dose escalate if no grade IV haematological toxicity observed.
- Temozolomide 200mg/m^2, once a day, orally, day 1-5.

**Dosing guidelines and modifications**
- Toxicities are graded according to National Cancer Institute-Common Toxicity Criteria.
- Temozolomide should be taken on an empty stomach; i.e. 1 hour before food or 2 hours after food.
- Temozolomide should be swallowed whole. Do not chew or crush. Capsules can be opened if the patient is unable to swallow whole capsules; please consult the CCLG temozolomide factsheet for further information (Appendix D).
- Round to the nearest 5mg, capsule sizes available; 5mg, 20mg, 100mg, 140mg, 180mg, 250mg. A liquid preparation may be available in some hospitals.
- Doses of temozolomide should be reduced by 20% if neutropenia (<0.5×10^9/L) or thrombocytopenia (<50×10^9/L) occurs and persists for at least 7 days.
- Treatment should be discontinued if progressive disease, unacceptable toxicity occurs or at patient/family request.
Oral etoposide [41, 42, 44, 45]

Baseline evaluation
Baseline evaluation includes a complete medical history, general and neurological examination, and haematological and biochemical assessments. Medical and neurological examinations are performed prior to each cycle.

Starting criteria for each cycle
- **Cycle 1**: satisfactory recovery from all previous therapies, with ideally 4 weeks since the last dose of previous chemotherapy and/or radiotherapy.
- ANC ≥1×10⁹/L.
- Platelet count ≥100×10⁹/L (transfusion independent).
- Haemoglobin level ≥80 g/L.
- Serum creatinine ≤1.5 ULN.
- AST or ALT ≤2.5 ULN and total bilirubin ≤1.5 ULN (except in Gilbert’s syndrome).

FBC and biochemical profile should be monitored every 2 weeks and tailored to the individual once a stable dosing regimen has been achieved. If the starting criteria are not met, treatment can commence at the discretion of the treating clinician.

Cycle 1 (28 days) Etoposide IV solution given orally
- Etoposide 25mg/m², twice a day, orally, day 1-21.
- Solution should be prepared immediately prior to administration.
- Etoposide IV solution has an unpleasant taste and can cause oral mucosal irritation.
- Stability studies have demonstrated that orange juice, apple juice and lemonade can be effectively utilised to disguise the taste of the etoposide IV solution (Bristol-Myers Squibb Pharmaceuticals limited, personal correspondence).
- For administration with drinks please consult the CCLG etoposide factsheet (Appendix D).

Cycle 1 (28 days) Etoposide capsules
- Etoposide 70mg/m², total daily dose, orally, day 1-21.
- Administer the total daily dose divided into 2 doses e.g. 50mg am, 100mg pm.
- Dosing differs due to the difference in bioavailability of the IV and capsule preparations [76, 77].
- 50mg and 100mg etoposide capsules are available therefore, discontinuous dosing can be used to achieve the desired overall dose, even if this shortens the overall course to less than 21 days.
- The capsules should never be opened to administer the drug.
- Etoposide capsules should be swallowed whole. Do not chew or crush.
- If there is a change in the ability to swallow capsules consider converting to the IV solution orally and adjust doses accordingly (25mg/m², twice a day, see above).

Dosing guidelines and modifications
- Toxicities are graded according to National Cancer Institute-Common Toxicity Criteria.
• Etoposide should be taken on an empty stomach; i.e. 1 hour before food or 2 hours after food.
• A 50% dose reduction should occur if platelets are $75 \times 10^9/L \leq \text{to} \leq 100 \times 10^9/L$ or ANC is $0.75 \times 10^9/L \leq \text{to} \leq 1 \times 10^9/L$.
• Treatment should be discontinued if platelets are $<75 \times 10^9/L$ or ANC is $<0.75 \times 10^9/L$.
• Treatment should be discontinued if progressive disease, unacceptable toxicity occurs or at patient/family request.
Baseline evaluation
Baseline evaluation includes a complete medical history, general and neurological examination, and haematological and biochemical assessments. Medical and neurological examinations are performed prior to each cycle.

Starting criteria for each cycle
- Cycle 1: satisfactory recovery from all previous therapies, with ideally 4 weeks since the last dose of previous chemotherapy and/or radiotherapy.
- No nitrosoureas during the previous 6 weeks.
- No uncontrolled diarrhoea.
- ANC ≥1×10^9/L.
- Platelet count ≥100×10^9/L (transfusion independent).
- Haemoglobin level ≥80 g/L.
- Serum creatinine ≤1.5 ULN.
- AST or ALT ≤2.5 ULN and total bilirubin ≤1.5 ULN (except in Gilbert’s syndrome)
- No active >grade II diarrhoea or uncontrolled infection.

FBC and biochemical profile should be monitored weekly and tailored to the individual once a stable dosing regimen has been achieved. If the starting criteria are not met, treatment can commence at the discretion of the treating clinician.

Cycle 1 (21 days)
**Temozolomide**
- Temozolomide 150mg/m^2, once a day, orally, day 1-5.
- Temozolomide should be taken on an empty stomach; i.e. 1 hour before food or 2 hours after food.
- Temozolomide should be swallowed whole. Do not chew or crush. Capsules can be opened if the patient is unable to swallow whole capsules; please consult the CCLG temozolomide factsheet for further information (Appendix D).
- Round to the nearest 5mg, capsules available include; 5mg, 20mg, 100mg, 140mg, 180mg, 250mg. A liquid preparation may be available in some hospitals.

**Irinotecan**
- Irinotecan 50 mg/m^2, once daily, IV, day 1-5.
- Infuse over 1 hour and administer 1 hour after temozolomide.
- The administration of prochlorperazine on the same day as irinotecan has been associated with a higher incidence of akathisia and is therefore not recommended.
- Drugs known to inhibit (itraconazole, ketoconazole) or induce (i.e. carbamazepine, rifampicin, phenytoin and phenobarbital) cytochrome P450 3A4 may alter metabolism of irinotecan, so are best avoided.
- Aprepitant may increase the side effects of irinotecan and should be avoided.
- St Johns wart should not be administered as it may reduce the plasma levels of the active metabolite of irinotecan.
• Patients **must** be observed for 2 hours post irinotecan administration for evidence of cholinergic symptoms (i.e. diarrhoea, rhinitis, increased salivation, contraction of pupils, lacrimation, flushing, sweating, intestinal cramping).

**Dose modifications for subsequent cycles**

• Toxicities are graded according to National Cancer Institute-Common Toxicity Criteria.
• Doses are adjusted based on the most severe toxicity that the patient experiences.
• See Appendix E for dose adjustment table with TEMIRI.
• Treatment to be discontinued if progressive disease, unacceptable toxicity occurs or at patient/family request.
Supportive care

Guidelines for the management of Irinotecan induced diarrhoea

Prophylaxis
- In the absence of any contraindications (i.e. known allergies), commence cefixime prophylaxis 8mg/kg day (maximum 400mg) OD PD, 2 days prior to starting irinotecan and for 7 days following the start of chemotherapy (day-2 to day+7) to reduce the risk of late onset diarrhoea.

Early onset diarrhoea
- Early onset diarrhoea is defined as diarrhoea starting during or within 8 hours of the irinotecan infusion.
- Administer atropine 20mcg/kg (maximum 250mcg) IV as a single dose.
- If diarrhoea does not improve following administration of atropine then patients should be instructed to start treatment for late diarrhoea.
- Prophylactic treatment with atropine (20mcg/kg orally or IV, maximum 250mcg) should be adopted before the next administration of irinotecan if the acute cholinergic symptoms including early diarrhoea were severe during the prior cycle.

Late onset diarrhoea
- At the first sign of diarrhoea starting >8 hours after irinotecan administration, patients should begin intensive loperamide therapy as per the Children’s British National Formulary (cBNF).
- Oral hydration with large volumes of water and electrolytes should be prescribed during the whole diarrhoea episode.
- Loperamide prophylaxis and treatment of diarrhoea must be implemented according to local clinical practice.

Pneumocystis jirovecii (carinii) pneumonitis prophylaxis
- Prophylaxis should be administered as per local institute policy.

Granulocyte-colony stimulating factor (GCSF)
- GCSF is not recommended for the chemotherapy regimens outlined in this guideline.

Antiemetics
- Antiemetics are recommended and should be prescribed according to local practice.
- The administration of prochlorperazine on the same day as irinotecan has been associated with a higher incidence of akathisia and is therefore not recommended.
- Aprepitant may increase the side effects of irinotecan and should be avoided.
Response evaluation
Imaging following the commencement of treatment should be undertaken following 2-3 cycles of chemotherapy and repeated throughout treatment (Appendix A) every 3-4 cycles or as per clinical need e.g. if there is suspicion of progression or symptoms suggesting raised intracranial pressure. If there is documented progression then an alternate strategy recommended in these guidelines or an appropriate early-phase trial should be considered. Equally it may be appropriate not to offer further chemotherapy.
References


Appendix A Neuroradiology guidelines

It is essential that all new children’s brain tumour cases are imaged using a consistent and comprehensive protocol. This is to ensure that optimal diagnostic information can be obtained, consistency is maintained, and studies are directly comparable and that all brain tumour cases can be recruited into national CCLG driven tumour studies. It is equally important that follow up imaging is undertaken in a consistent and timely manner. Lack of a consistent protocol has led to very significant difficulties in analysing imaging of patients enrolled into CCLG tumour studies from different centres in the UK.

Pre-surgery

Brain

- Standard sequences
  - Axial T1, T2
  - Coronal FLAIR
  - DTI and/or DWI (with ADC maps)
  - Post Gd Ax, Cor, Sag T1: at 1.5T
  - Post Gd Ax T1, Ax 3D T1 volume: at 3T (Use MP-RAGE T1w+gad 1.0 mm slices for radiotherapy planning)

- Optional sequences (according to local capacity/availability or CCLG trial involvement)
  - Cor/SagT2 or FLAIR
  - Perfusion MRI (requires placement of blue or pink cannula)
  - ASL
  - MRS

Spine

- Standard sequences
  - Sag T1 (post Gd)
  - Ax T1 through any equivocal focal abnormality

Optional

- Sag T2

Immediately post-operatively (ideally within 48 hours)

Brain

- Standard sequences
  - Ax T1, T2,
  - Coronal FLAIR
  - DTI and/or DWI (with ADC maps)
  - Post Gd Ax, Cor, Sag T1: at 1.5T
  - Post Gd Ax T1, Ax 3D T1 volume: at 3T

Spine (only if not obtained prior to surgery)

- Standard sequences
  - Sag T1
  - Ax T1 through any equivocal focal abnormality
Follow-up examinations

Brain
- Standard sequences
  - Axial T1, T2
  - Coronal FLAIR
  - DTI and/or DWI (with ADC maps)
  - Post Gd Ax, Cor, Sag T1: at 1.5T
  - Post Gd Ax T1, Ax 3D T1 volume: at 3T
- Optional (according to local preference or CCLG trial involvement)
  - Cor/Sag T2 or FLAIR
  - Perfusion MRI (requires placement of blue or pink cannula) ASL
  - MRS if tumour size >1.0cm (and dependent on tumour type/protocol)

Spine (dependent on tumour type/protocol)
- Standard sequences
  - Sag T1, (post Gd)
  - Ax T1 through any equivocal focal abnormality
- Optional
  - Sag T2
Appendix B Centralised Molecular Diagnostics and Pathology Review of Medulloblastoma: National Reference Centre open for submissions

On behalf of the NCRI Childhood Cancer CSG Brain Tumour Subgroup, the CCLG CNS Tumours Special Interest Group and the SIOP-Europe Brain Tumour Group, we are pleased to write to inform you that we are now able to make available centralised molecular pathology for all medulloblastoma patients under the care of UK centres.

As you will be aware, these services have been piloted in the recent CCLG Medulloblastoma Feasibility Study, and are now in place to support enrolment of children onto the SIOP-PNET5-MB clinical trial, which is open in the UK and is currently in the process of being rolled out to all centres. Many centres are actively submitting samples to these studies, and we thank you for this ongoing involvement. In addition, the referral practices of Prof Tom Jacques (Great Ormond Street Hospital, London) and Dr Abhi Joshi (Royal Victoria Infirmary, Newcastle) have been providing second opinions, based on contemporary molecular diagnostics, for many centres in recent years.

We have recently received generous funding from The Brain Tumour Charity to unify these services and to extend them to all medulloblastoma patients in the UK, such that they will be made available free-of-charge to submitting treatment centres for the next two years (to December 2019). We will seek to establish sustainable funding for these services by the end of this two-year period, in consultation with NHS Commissioners, Local Centres and the NCRI, CCLG and SIOP-E working groups; and in concert with the National rearrangement of NHS genomic services which is taking place throughout 2018.

The SIOP-PNET5-MB service is coordinated by the National Medulloblastoma Reference Centre (Prof Steve Clifford, lead) at the NHS Department of Cellular Pathology at the Royal Victoria Infirmary, Newcastle. It encompasses central pathology review by the UK neuropathology panel (Dr Abhi Joshi, Dr Simon Paine, Prof Tom Jacques) and molecular tests currently delivered by the accredited laboratories of the Northern Regional Genetics Service, Newgene Ltd., and Great Ormond Street Hospital for Children NHS Foundation Trust. The extension of this service will provide a common entry point to the forthcoming SIOP-E High-risk medulloblastoma trial, upon its planned opening in 2019. Non-trials samples may be submitted directly to either Prof Tom Jacques or Dr Abhi Joshi for central assessment/second opinion.

Submission of samples

(i). Assessment of eligibility for SIOP-PNET5-MB or HR-MB trials
Samples should be notified and submitted as per the SIOP-PNET5-MB guidelines (attached).

(ii). Non-trials patients
Samples should be notified and shipped to either Dr Abhi Joshi or Prof Tom Jacques as an urgent referral and tissue sent to them according to the attached guidelines.
Contacts and shipping details for non-trials patients

Please send to either:
Royal Victoria Infirmary, Newcastle (referral to Dr. Abhi Joshi)

Dr Abhi Joshi
Consultant Neuropathologist
c/o Janet Thompson
Neuropathology Department
Cellular Pathology
Level 3, New Victoria Wing
Royal Victoria Infirmary
Newcastle Hospitals NHS Foundation Trust
Queen Victoria Road
Newcastle upon Tyne
NE1 4LP

Tel: 0191 2821959
Emails:
Abhijit.Joshi@nuth.nhs.uk
Janet.Thompson9@nuth.nhs.uk
s.crosier@nhs.net

Great Ormond Street Hospital, London (referral to Prof Tom Jacques)

Prof Thomas Jacques
Consultant Neuropathologist
Department of Histopathology
Great Ormond Street Hospital NHS Foundation Trust
Camelia Botnar Laboratories
85 Lamb’s Conduit Street
LONDON
WC1N 3NN

Tel: 0207 8298663
Email: gosh.histopathology@nhs.net

Non-trials samples - If Frozen and FFPE is available:
On the establishment of a local diagnosis of medulloblastoma to WHO (2016) histological criteria. Please contact the Newcastle or London laboratories via email, or by telephone.

A courier PDP providing packaging and dry ice will be organised by the Newcastle or London team to collect the frozen tissue, FFPE blocks, and sample paperwork (Copy of the pathology report, Referral paperwork and any local material transfer documentation which you use for tracking samples) from your laboratory reception.
Please note: The repertoire of molecular tests provided by the National centre have the highest success rate in frozen tissue, submission of which is a mandatory component of the SIOP-PNET5-MB clinical trial and the forthcoming SIOP-E High-risk medulloblastoma trial.

**Non-trial samples - If only FFPE tissue is available:**
Please contact the Newcastle or London laboratories via email, or by telephone.

FFPE tissue blocks and paperwork (Copy of the pathology report, Referral paperwork and any local material transfer documentation which you use for tracking samples) should be sent via your local registered postal service to the shipping address above.

The repertoire of molecular tests provided by the National centre can still be performed on FFPE, though the risk of test failure is higher.

**Testing repertoire**
The following tests form the current repertoire available at the National reference centre:

- Histopathological review, immunophenotype and molecular subgroup (to include H&E, reticulin, GFAP, synaptophysin, neurofilament, p53, INI-1 (BAF47), beta-catenin, EMA, Lin28, Ki-67 (MIB-1), p75-NGFR (or GAB1), OTX2 and YAP1 immunostains).
- Medulloblastoma molecular subgroup status by a second method (850K DNA methylation array or MassArray).
- Mutational status of CTNNB1 and TP53.
- Copy number status of MYC, MYCN (mandatory) and chromosome 6 (by FISH or SNP array).

The system is modular and new validated tests will be added in line with future developments in practice and/or amendments to clinical trials, to maintain a contemporary service. For instance, panel and germline sequencing of medulloblastoma-associated genes (e.g. PTCH1, SUFU, APC, BRCA2, PALB2) are currently under development, for implementation in 2018.

All tests are developed and executed in conjunction with guidelines and quality control exercises governed by the SIOP-E Brain Tumour Group. Additionally, quality control exercises are undertaken between the Newcastle and London labs.

**Turnaround time, reporting, tumour banking and interaction with local centres**
Current average turnaround times are 15-20 days to reporting from receipt at the National Reference Centre. For clinical trials-eligible cases, results will be communicated through the standard trials-associated proforma (CRFs). For non-trials and trials-ineligible patients, an integrated referral opinion/report will be issued by the Consulting Central Review Neuropathologist (Joshi, Paine, Jacques), in close consultation with the submitting Local Centre Neuropathologist. Clinical trials samples will be registered with the CCLG Biobank and the trial biological study, as mandated within the trial protocol. Non-trials samples will be registered to the CCLG Biobank, as appropriate following consultation with the Local Centre.
We are sure you will all agree that this is a very exciting and important step in the nationwide contemporisation of medulloblastoma diagnostics, which has only been made possible by the enthusiastic support of the UK Childhood Cancer clinical community. We look forward to your continued engagement, and are ready to work with you to receive your samples for assessment.

Please do not hesitate to get in touch if need further information or have any questions.

With very best wishes,

Prof Steve Clifford  
Lead, National Medulloblastoma Reference Centre & SIOP-E Medulloblastoma Biology Group

Prof Tom Jacques  
Consultant Neuro-pathologist, National Medulloblastoma Reference Centre

Dr Abhi Joshi  
Consultant Neuro-pathologist, National Medulloblastoma Reference Centre

Dr Nicky Thorp  
Chair, CCLG CNS Tumours Special Interest Group

Prof Simon Bailey  
Chair, NCRI Childhood Cancer CSG Brain Tumour Subgroup & CCLG Embryonal Tumours Group

This initiative is generously supported by The Brain Tumour Charity. As part of our funding, we believe everyone should have access to the best support and information available to help them following the devastating news of a brain tumour diagnosis. To access the resources you require, including posters and leaflets about our services and brainy bags (a free gift for children with a diagnosis) contact us at childrenandfamilies@thebraintumourcharity.org or call us on 0808 800 0004. Our support services help people to live their life well with improved quality of life through reducing isolation, increasing ability to cope and helping maintain independence. We have dedicated support teams who develop information resources, provide direct and peer-to-peer support platforms (online and on the phone), provide digital support and information sharing opportunities and run information and dedicated family events across the UK. We have specific services that are designed to support adults, young adults and children and families. Visit our website www.thebraintumourcharity.org to find out more about our support services.
Appendix C Medicines information

Mechanisms of action

Temozolomide
- Alkylating agent.

Etoposide
- Topoisomerase II inhibitor – causes error in DNA synthesis promoting apoptosis.

Irinotecan
- Topoisomerase I inhibitor - obstructs DNA replication in the S-phase of the cell cycle.

Drug Interactions

Temozolomide
- Increased sodium valproate levels occur due to reduced clearance with temozolomide.

Etoposide
- Caution is advised with concomitant use of etoposide and inducers or inhibitors of cytochrome P450 3A4 and are therefore best avoided.

Irinotecan
- Drugs known to inhibit (itraconazole) or induce (i.e. carbamazepine, rifampicin, phenytoin) cytochrome P450 3A4 may alter metabolism of Irinotecan, so are best avoided.
- St Johns wart should not be administered with irinotecan as may reduce the plasma levels of the active metabolite of Irinotecan.
- Avoid phenothiazine derivatives (levomepromazine) due to increased incidence of akathisia.

Side effects

Temozolomide
- Common; gastrointestinal (constipation, nausea and vomiting), neurological (headache, seizures) and fatigue.
- Serious; hepatotoxicity, haematological (myelosuppresion, neutropenia and thrombocytopenia).
- For full details consult the product literature.

Etoposide
- Common; gastrointestinal (nausea and vomiting).
- Serious; haematological (myelosuppresion, neutropenia and thrombocytopenia).
- For full details consult the product literature.
Irinotecan

- Common; gastrointestinal (diarrhoea, nausea and vomiting), haematological (neutropenia and anaemia), hepatic (transient mild to moderate increases in serum levels of transaminases, alkaline phosphatase or bilirubin).
- Serious; transient acute cholinergic syndrome (i.e. diarrhoea, rhinitis, increased salivation, contraction of pupils, lacrimation, flushing, sweating, intestinal cramping).
- For full details consult the product literature.
Appendix D Drug factsheets for patients and families

Temozolamide

https://www.cclg.org.uk/write/MediaUploads/Publications/Drug%20Factsheets%20(PDFs)/Drug_Factsheet_Temozolomide_Web.pdf

Etoposide

https://www.cclg.org.uk/write/MediaUploads/Publications/Drug%20Factsheets%20(PDFs)/Drug_Factsheet_Etoposide_Web.pdf
### Appendix E Dose adjustment tables for TEMIRI regimen

<table>
<thead>
<tr>
<th></th>
<th>Temozolomide</th>
<th>Irinotecan</th>
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<tr>
<td><strong>Starting dose</strong></td>
<td>Reduction (20%) dose level 1</td>
<td>Reduction (20%) dose level 1</td>
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<tr>
<td>150 mg/m², day 1-5</td>
<td>120 mg/m², day 1-5</td>
<td>90 mg/m², day 1-5</td>
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<td>50 mg/m², day 1-5</td>
<td>40 mg/m², day 1-5</td>
<td>30 mg/m², day 1-5</td>
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<table>
<thead>
<tr>
<th><strong>Type of toxicity</strong></th>
<th><strong>Dose modification at first occurrence</strong></th>
<th><strong>Dose modification at second occurrence</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>ANC &lt;1×10⁹/L or platelet count &lt;100×10⁹/L but recovered on day 21 after the start of a cycle.</td>
<td>No modification.</td>
<td>No modification.</td>
</tr>
<tr>
<td>ANC &lt;1×10⁹/L or platelet count &lt;100×10⁹/L but recovered between day 22-28 after the start of a cycle.</td>
<td>Decrease temozolomide to dose level 1.</td>
<td>Decrease temozolomide to dose level 2. Decrease irinotecan to dose level 1.</td>
</tr>
<tr>
<td>ANC &lt;1×10⁹/L or platelet count &lt;100×10⁹/L but recovered between day 29-34 after the start of a cycle.</td>
<td>Decrease temozolomide to dose level 1. Decrease irinotecan to dose level 1.</td>
<td>Decrease temozolomide to dose level 2. Decrease irinotecan to dose level 2.</td>
</tr>
<tr>
<td>ANC &lt;1×10⁹/L or platelet count &lt;100×10⁹/L on day 34 after the start of a cycle.</td>
<td>Discontinue treatment.</td>
<td>Not applicable.</td>
</tr>
<tr>
<td>Grade III and IV diarrhoea despite maximum loperamide therapy.</td>
<td>Decrease irinotecan dose to dose level 1. If the same level of toxicity persists &gt;2 weeks despite symptomatic treatment, discontinue treatment. If diarrhoea is ongoing on day 21, delay next cycle for up to 2 weeks until diarrhoea resolves to ≤ grade I. If the diarrhoea does not resolve after a 2-week delay, discontinue treatment.</td>
<td>Decrease irinotecan to dose level 2. If the same level of toxicity persists &gt;2 weeks despite suitable symptomatic treatment, discontinue treatment. If diarrhoea is ongoing on day 21, delay next cycle for up to 2 weeks until diarrhoea resolves to ≤ grade I. If the diarrhoea does not resolve after a 2-week delay, discontinue treatment.</td>
</tr>
<tr>
<td>Other grade 3 non-haematological toxicity. *</td>
<td>Decrease both irinotecan and temozolomide to level 1.</td>
<td>Discontinue treatment.</td>
</tr>
<tr>
<td>Other grade 4 non-haematological toxicity. *</td>
<td>Discontinue treatment.</td>
<td>Not applicable.</td>
</tr>
</tbody>
</table>

*For toxicities that are manageable or short-lived (i.e. grade 3-4 electrolyte abnormalities amenable to supplementation or grade 3 fatigue < 72 hours), the doses are not to be decreased.