A PROSPECTIVE RANDOMISED CONTROLLED TRIAL OF HYPERFRACTIONATED VERSUS CONVENTIONALLY FRACTIONATED RADIOTHERAPY IN STANDARD RISK MEDULLOBLASTOMA

HIT – SIOP PNET 4

A SIOP and GPOH TRIAL

START DATE 1st September 2003

An Extension of the Trial –
HIT 2000 AB 4
START DATE 1st January 2001

CNS 2003 05
UK START DATE – 1st December 2003

Version 3, 27th July 2010
(RG_10-034)

HIT-SIOP PNET 4 (CNS 2003 05)

Protocol amendments
Amendment 1 : 1 June 2004

These amendments are necessary following discussion within the PNET 4 study committee, following an investigator meeting for PNET 4 and following comments received from users of the protocol.

1. At the request of the SIOP Scientific Committee in September 2002 a disclaimer indicating that SIOP is not a clinical trials organisation and therefore cannot be held responsible for the overall conduct of the study, has been added.

2. On flow chart 1.2 - entry procedure, the question mark, after the residual tumour >1.5cm^2, has been removed. This is to avoid confusion.

3. The late effects schema for the study as reflected in 1.5 and in the body of the text has been changed. This is to make clear the timing on the late effects studies and to ensure that they match the timing indicated on the questionnaires themselves.

4. Redundant references in relation to late effect studies have been removed.

5. Over the last year the PNET 4 study committee have considered the issue of large cell medulloblastoma. There have been recent papers indicating that large cell medulloblastoma, a rare subtype of medulloblastoma comprising <5% of cases, carries a poor prognosis and as such should be considered high risk tumours. In this respect large cell medulloblastoma are no longer eligible for entry into the study.

6. The eligibility criteria have, with respect to the timing of radiotherapy, been changed to avoid confusion. The current recommendation is that there is an <u>intention</u> to start radiotherapy no more than 40 days after surgery.

7. The consent for biological studies was incorrect in the previous version of the protocol. The consent for the biological studies specific for the study is obtained at the same time as consent for entry into the study itself. This was approved by the MREC. We still, however, strongly recommend that consent also be obtained for banking of tumour specimens under the general UKCCSG for tumour banking (MREC 98/04/013).

8. In the radiotherapy section the statement with regard to the timing of radiotherapy has been changed to say that radiotherapy should, <u>wherever possible</u>, begin within 40 days.

9. With regard to serious adverse events, the wording has been changed slightly, consistent to that used in other CCLG studies ie. defining an SAE as an unexpected medical occurrence and stating that death from tumour progression is <u>not</u> an SAE. With regard to reporting of

SAEs the wording has been changed to state that SAEs must be reported within 24 hours of knowledge of the event.

10. Dr Richard Gilbertson has resigned from the study committee. His name has been removed from the list of contacts details for committee members and from the flow sheets relating to processing of material.

11. With regard to the information sheets, text has been added relating to the late effects questionnaires and endocrine studies. In addition the information about the start time of radiotherapy has been changed and states that radiotherapy should generally start no longer than 40 days after surgery. This is in recognition that some patients who are randomised into the study will not be able to start their radiotherapy within 40 days or less.

Amendment 2

Protocol Version 3.0_27th July 201

1. Updated contact details to relect the transfer of UK Trial Managment and Sponsorship from the CCLG (formally UKCCSG) Data Centre, University of Leicster to the Cancer Research UK Clinical Trials Unit (CRCTU), University of Birmingham

2. Removal of Patient Information Sheets, Consent Forms and GP Information Sheet from the protocol. These will continue to exist as stand alone documents.

3. The additon of cross-sectional quality of survival data collection to begin October 2010 (section 4.7.3.1).

4. Changes to the booklet age ranges of the questionnaires to be completed for the cross-sectional data collection. (Appendix M)

THE HIT-SIOP PNET 4 STUDY

The Brain Tumour Committee of the International Society of Paediatric Oncology (SIOP) has been responsible for the development of a number of international multi-centre studies for tumours of the central nervous system (CNS) in children and adolescents. Studies developed by the SIOP Brain Tumour Committee include those for medulloblastoma/PNET, ependymoma and germ cell tumours. Three previous studies, namely SIOP 1, SIOP 2 and PNET 3 have been specifically designed for patients with medulloblastoma/PNET.

Since 1999 the PNET working group of the SIOP Brain Tumour Committee have met to discuss and develop a successor to the PNET 3 study that closed in 2001. It was hoped that this new study, PNET 4, would be a collaborative venture involving a significant number of national tumour groups. The PNET working group felt that the priority was to develop a study for standard risk (SR) medulloblastoma (MB) in children at least 3-5 years of age, the treatment for which involves both craniospinal radiotherapy (CSRT) and chemotherapy (CT).

The SIOP PNET group considered a number of possible questions to address in a randomised controlled trial. After discussion it was felt that the pre-eminent question would be that investigating the benefit of hyperfractionated radiotherapy (HFRT) i.e. a randomised comparison between conventionally fractionated and HFRT with both arms being followed by identical standard chemotherapy with 8 courses of cisplatin, CCNU and vincristine.

It was recognised by the SIOP PNET group that the proposed PNET 4 study was based essentially on the work of the German HIT study group that had begun to design a very similar prospective randomised study in 1998 addressing the same question. Thus a randomised comparison of conventionally fractionated RT vs HFRT formed the basis for the study in SR MB incorporated into the HIT 2000 group of studies. The HIT 2000 AB 4 study for SR MB commenced in January 2001 and to date (July 2003) has accrued approximately 85 patients randomised between the 2 treatment arms.

With the recognition that the proposed PNET 4 study was similar to that for SR MB in the HIT 2000 study, discussions have taken place as to ways in which to enable patients with SR MB from the HIT group as well as other national groups to be entered in a study or studies of conventionally fractionated RT v HFRT with data being jointly analysed. It was initially intended by the HIT group to submit data from the HIT 2000 AB 4 study into the database of the PNET 4 study that would be developed for the other national tumour groups. It was, however, felt that this solution was not viable for a number of reasons including the fact that the HIT group patients would essentially be entered into a very similar but two distinct randomised control trials. A further option was to close the HIT 2000 study for SR MB at the point at which a new study, PNET 4, opened. This was understandably unacceptable to the HIT group, again for a number of reasons, including the fact that data from patients already randomised into HIT 2000 would be lost. The agreed solution to this dilemma is to convert HIT 2000 AB 4 into a new protocol to be called HIT-SIOP PNET 4. Such a conversion can be achieved because the proposed PNET 4 study and the HIT 2000 AB 4 study are almost identical in terms of the study design e.g. end points, eligibility criteria, treatments employed and secondary studies ie. biological and late effects studies. Following conversion of the HIT 2000 AB 4 study into the common protocol, HIT-SIOP PNET 4, other national groups would enter this study.

The advantages for such a conversion are that patients with SR MB from a number of national tumour groups including those from Germany, Austria, France, UK, Spain, Nordic countries, Belgium, Switzerland and the Netherlands could be entered into a single protocol increasing the likelihood that sufficient patients will be accrued to answer the important primary question. In addition the increased number of patients would be entered into common secondary studies addressing important issues such as the prognostic evaluation of biological markers and the determination of late effects associated with therapy.

The GPOH and the participating countries of the proposed PNET 4 study approved the extension and modification of HIT 2000 AB4 into a common study. The essence of the new common protocol, HIT-SIOP PNET 4, is as follows:

1. There will be one trial ie. no parallel trials of HIT 2000 and SIOP PNET 4 as initially considered.

2. HIT 2000 AB 4 will be modified to a new common protocol HIT-SIOP PNET 4. As HIT-SIOP PNET 4 is a modification of HIT 2000 AB 4, the official start date of the trial is January 1st 2001, the start date of HIT 2000 AB 4.

3. All patients randomised from January 1st 2001 will be included in the final analysis.

4. Parents of patients registered previously into HIT 2000 AB4 will be asked to sign a data consent form covering additional components of HIT-SIOP PNET 4.

5. Modifications to HIT 2000 AB 4 to be incorporated into the new common protocol are as follows:

    a) the boost to post-operative residual tumour will be omitted.
    b) The statistical section of HIT 2000 AB 4 will be modified in accordance to the increased patient to be entered into the common protocol.
    c) The international data centre will be in Stockholm, Sweden. The governing body of the common protocol will be revised (appendix A) as will the logistics of running the trial (appendix B).
    d) The secondary questions for the proposed PNET 4 study will be adopted.
    e) There will be only one external independent data monitoring committee that will be re-constituted.
    f) Individual national groups will have a right to perform a separate final analysis of their patients data after the final analysis of the total number of patients within HIT-SIOP PNET 4
    g) National groups will not perform separate analyses that might possibly harm patient accrual into HIT-SIOP PNET 4.

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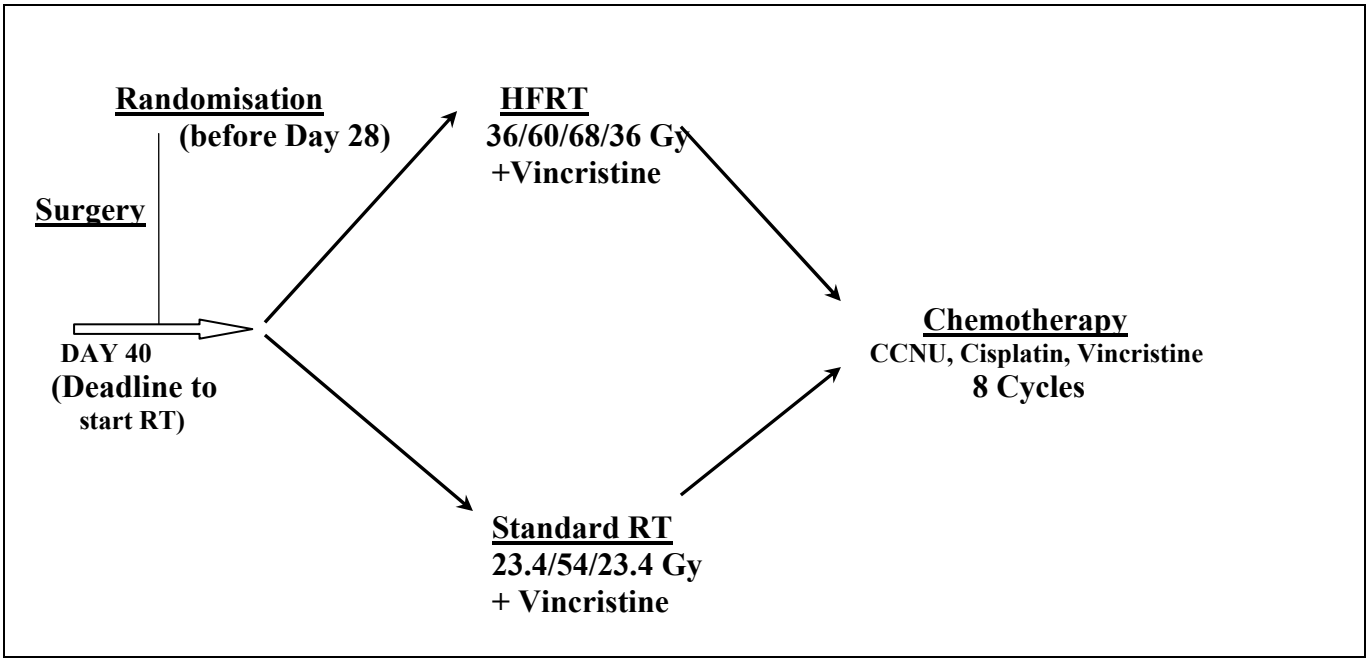
1. FLOW DIAGRAMS

1.1 Summary of the Study



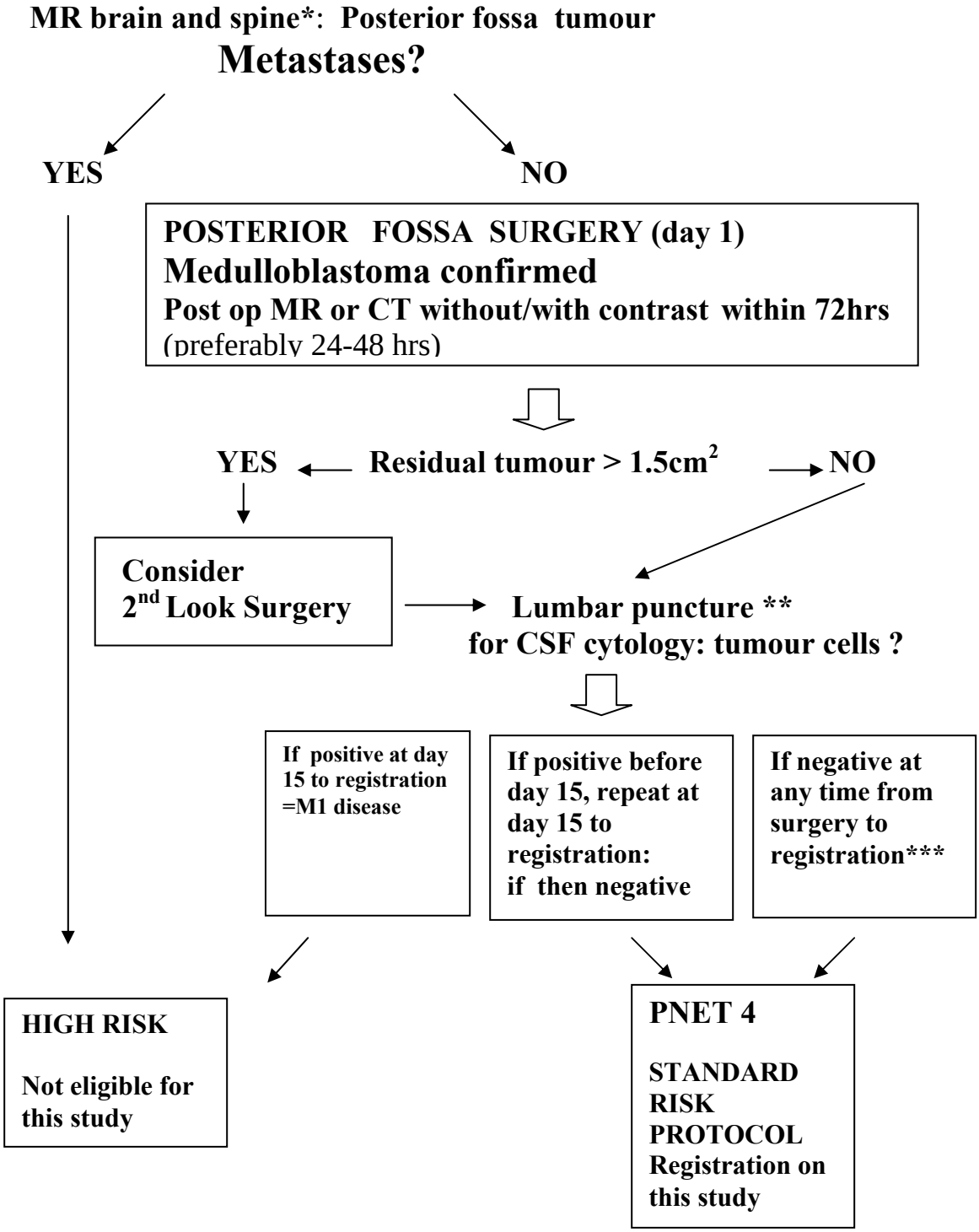
This protocol has been reviewed by the SIOP Scientific Committee in September 2002 and approved as a SIOP clinical trial in regard to the importance of the questions being addressed and the quality of the science. However, SIOP is not a clinical trials organisation and therefore cannot be held responsible for the overall conduct of the study which rests with the treating physicians and each individual country's childhood cancer trials organisation.

With this protocol the GPOH and the SIOP PNET 4 Study Commitee presents a a randomised trial for the treatment of standard risk medulloblastoma in children and adolescents. Possible changes or amendments to the protocol will be communicated by the appropriate National Co-ordinator to participating institutions. Participating centers are requested to ensure the validity of their available protocols.

Centres wishing to participate in the PNET 4 study should be able to comply with every aspect of the study protocol including all the quality control procedures.

The Study Commitee emphasizes that even following approval from the ethics committees of paticipating centres, no legal responsibility for possible consequences resulting from the application of recommendations from this protocol will be taken by the members of the study committe. Treatment and follow-up of patients with medulloblastoma requires a high degree of medical care existing only in hospitals with adequate infrastructure. Significant complications from the underlying disease or from its treatment can develop in every patient at any time and may require a full range of resources including intensive care. Children with medulloblastoma should thus be treated by an experienced team and interdisciplinary cooperation is a prerequisite for such a team including experienced neurosurgeons, neuropathologists, neuroradiologists, radiotherapists, pediatricians and nurses.

1.2 Entry Procedure

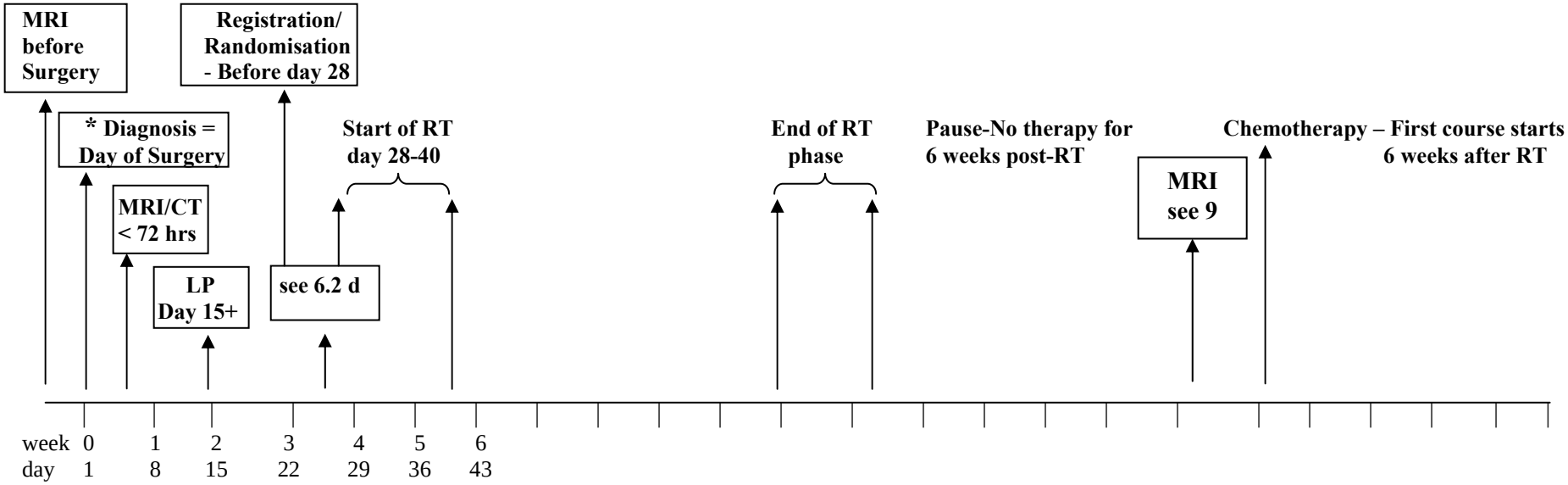


*MR spine should preferably be performed preoperatively but may be performed postoperatively at any time before registration

** If lumbar CSF cytology was positive for tumour cells at any time before day 15 this finding needs to be confirmed by lumbar puncture at day 15 or later until registration, thus avoiding registering a temporary postoperative tumour cell leakage as M1 disease.

***If lumbar puncture is performed for any reason before day 15 and is negative it need not be repeated.

1.3 Flow diagram for investigation and treatment



Data Form: **F1-F4 F5-F6** **F7** **F8 x 8**

week (RT+Vincristine)	0	1	2	3	4	5	6	7
day (RT+Vincristine)	1	8	15	22	29	36	43	50
Vincristine 1.5 mg/m^2	**V**	**V**	**V**	**V**	**V**	**V**	**V**	**V**

*** Inform department of radiation oncology as soon as possible after diagnosis to avoid any delay in starting radiotherapy.**

<u>Chemotherapy</u> **8 Cycles given at 6 weekly intervals**

V – Vincristine 1.5 mg/m^2 (maximum 2 mg)
C – Lomustine (CCNU) 75 mg/m^2
P - Cisplatin 70 mg/m^2

Weeks
1 2 3 4 5 6
V------V------V------ ------ ------ ------
C
P

1.4 Schema for investigations before chemotherapy (see10.2)

	MRI	FBC	Blood Biochemistry	GFR	Audiology
Course 1	x	x	x	x	x
Course 2		x	x		x
Course 3		x	x	x	x
Course 4		x	x		x
Course 5	x	x	x	x	x
Course 6		x	x		x
Course 7		x	x	x	x
Course 8		x	x		x

These are the minimal investigations to be performed.
More frequent monitoring (e.g. for renal function) or additional investigations may need to be performed on an individual basis.

1.5 Schema for tumour monitoring and late effects follow up.

Timing relative to diagnosis Assess-ment	Post Surgery + Before RT	End of Chemo-therapy	2 yrs	3 yrs	4 yrs	5 yrs	6+ yrs	Age 20 years[9]
MRI and disease status dataform 12	*[1]	*[1] q. 6 m form 12	*[1] q. 6 m form 12	*[1] form 12	*[1] form 12	*[1] form 12	form 12	form 12
Neurology, audiology, health and education dataforms 3, 5, & 11	*[2] forms 3, 5	*[2] form 11		*[2] form 11		*[2] form 11		*[2] form 11
Endocrin-ology dataforms 5, 9,10	*[3] form 5	*[3] forms 9, 10	*[3] form 9	*[3] forms 9,10	*[3] form 9	*[3] forms 9, 10	*[3] form 9, and annually thereafter until 20 years old	*[3] forms 9, 10
HUI in booklet *[4]	*[5]	*[5]		*[5]		*[5]		*[6]
SDQ in booklet *[4]	*[5]	*[5]		*[5]		*[5]		*[10]
QoL in booklet *[4]	*[7]	*[7]		*[7]		*[7]		*[8]

1 = MRI: After end of chemotherapy. Then at least every 6 months until 3 years post therapy. Thereafter at physician's discretion.

2 = Form 3 is for completion by neurosurgeon, forms 5, 11 by physician/nurse. For audiology, see section 4.7.6 and 10.4.4. At the end of therapy, a Pure Tone Audiogram will be performed and the Brock grading recorded on the appropriate data form or a hard copy of this audiogram sent to the National Data Centre.

3 = See Appendix M (section C) which details the minimum data to be recorded and reported.

4= HUI, SDQ and country-specific QoL forms for completion by (a) older patients and (b) a parent/carer have been compiled into age-appropriate booklets in most relevant European languages and will be supplied by national data-centres

5 = Parent and, if aged 11 years or more, patient.

6 = Patient and, if appropriate, parent/carer.

7 = Parent and, if > 11 years, patient. CHQ PF 28 (Germany and UK only) plus one of PedsQL or PEDQOL according to national choice – Optional.
8 = Patient- QLQ-C30 including BN 20 in all 20 year olds– Mandatory.
9 = The assessment at 20 years is irrespective of interval from diagnosis and the pubertal and auxology data should be recorded annually until aged 20y. In patients enrolled after reachingthe age of 16, there will also be the assessments until 5 years from diagnosis some of which will occur past the age of 20 years.

Final auxology (height, sitting height, weight and pubertal status) hormone and hormone treatment data should be recorded and reported around the age of 20 years.
10 = Patient and, if appropriate, parent/carer (UK only).

2. SYNOPSIS

This is an international prospective randomised trial, which will compare two radiotherapy regimens in children and adolescents (aged 4 or 5 years [section 5.1] to 21 years inclusive) with carefully staged 'standard risk' medulloblastoma. Patients eligible for the study will be those with non-metastatic medulloblastoma (by imaging and CSF cytology) at diagnosis. Patients randomised to the standard arm will receive conventionally fractionated (once a day) radiotherapy with a dose of 54 Gy to the posterior fossa and 23.4 Gy to the craniospinal axis. The experimental arm will be hyperfractionated (twice a day) radiotherapy (1 Gy b.d.) with a dose of 60 Gy to the posterior fossa with an additional 8 Gy to the tumour bed and 36 Gy to the craniospinal axis. Both groups will receive identical chemotherapy consisting of eight weekly doses of Vincristine given with radiotherapy and 8 courses of CCNU, cisplatin and vincristine following radiotherapy.

The primary objective of the study will be a comparison of event free survival between the two treatment arms. Secondary objectives will be to compare overall survival and the pattern of relapse between the treatment arms and to examine and compare between the two arms the late effects of treatment, with focus on health status, audiological and endocrine toxicity. Toxicity of surgery and its impact will be systematically documented. In addition, and importantly, a number of biological studies will be undertaken to examine in a prospective fashion a range of molecular aberrations with the aim of identifying markers which may allow more accurate risk stratification for patients with clinically defined standard risk medulloblastoma.

3. AIMS and OBJECTIVES

Primary Objective:

To compare in a randomised trial the event free survival rate for children and adolescents with standard risk medulloblastoma treated with either hyperfractionated radiotherapy or reduced dose radiotherapy with conventional fractionation.

Secondary Objectives:

a) To compare overall survival between the two treatment arms.

b) To compare the pattern of relapse between the two treatment arms with particular respect to

local relapse (tumour bed, posterior fossa outside tumour bed).

c) To explore the benefit and the risks of neurosurgery:

i) To determine the toxicity of surgery.
ii) To investigate whether there are identifiable factors that correlate with toxicity.
iii) To define the impact of any complications of surgery on commencement of adjuvant therapy and on EFS.

d) To compare the late sequelae in the two treatment arms with focus on Health Status, endocrine deficiencies and hearing loss.

e) To perform prospective biological studies

i) To identify important molecular prognostic markers of use for routine disease risk stratification of children with clinically defined standard risk medulloblastoma. Molecular abnormalities investigated will include:

- Loss of 17p ± gain of 17q.
- Loss of 9q22.
- ErbB2 and ErbB4 receptor co-expression.
- *MYC* oncogene amplification /over expression.
- Expression of TrkC.

ii) To increase understanding of the role played by the interaction of these molecular aberrations in medulloblastoma disease behaviour and treatment responsiveness.

iii) To establish the feasibility of performing multi-centre collection of freshly resected tumours for central RNA analysis using a room temperature storage protocol.

4. RATIONALE

4.1 Medulloblastoma

Medulloblastoma is a highly cellular malignant embryonal neoplasm classified as a Primitive Neuroectodermal Tumour (PNET)[1]. It is the most common malignant brain tumour in childhood, accounting for between 15 and 20 % of all childhood primary central nervous system (CNS) neoplasms. By definition, medulloblastoma arises in the posterior fossa, usually from the cerebellar vermis in the roof of the 4th ventricle. As with other PNETs, medulloblastomas have a marked propensity to seed within the CSF pathways, with evidence of such metastatic spread occurring in up to 35 % of cases at diagnosis.

Over the last thirty years, various national and international groups have conducted studies to refine and improve the treatment of medulloblastoma. Such studies have focused on three main areas:

- definition of risk groups and subsequent modification of therapy based on such groupings.
- investigation of the role of chemotherapy administered either before and/or after craniospinal

radiotherapy.
- investigation of a reduction in the dose of craniospinal radiotherapy in standard risk patients.

4.2 Staging and the concept of standard risk medulloblastoma

It is clear that the prognosis of medulloblastoma is most closely related to the age of the patient, to the extent of disease at diagnosis and to the dose and volume of radiotherapy. Patients with disseminated disease, as well as very young patients (e.g. less than three years of age), have a much poorer prognosis than other patients. Because of the worse prognosis in very young children and the unacceptable sequelae associated with craniospinal radiotherapy (CSRT), recent therapy in children aged less than 3 to 6 years has focused on the use of so called 'Baby Brain' protocols. These treatment regimens utilise prolonged administration of chemotherapy in order to delay or avoid the use of radiotherapy and in particular to avoid the use of whole neuraxis radiotherapy [2 3 4]. Therefore such young children are not eligible for the present study.

4.2.1 Metastatic disease

With regard to the extent of disease, the presence of metastatic disease at presentation as diagnosed by the presence of meningeal enhancement on MRI of the brain (Chang Stage M2) or spine (Chang Stage M3)[5] clearly carries a poor prognosis. The prognostic significance of Chang Stage M1 disease, in which tumour cells are found within the CSF without radiological evidence of metastasis, is less clear, although several studies for example, CCG-921 (see below) have shown that patients with M1 disease do have a worse prognosis than those without evidence of such tumour spread[6 7 8]. The poorer outlook for patients with M1 disease is now widely accepted by the North American Children's Oncology Group (COG), with these patients regarded as being high-risk patients. Likewise, the SIOP Brain Tumour Committee now accept that patients with M1 disease cannot be regarded as standard risk, and are thus not included in the study described in this protocol.

4.2.2 Residual disease

With regard to local disease, some studies have demonstrated the prognostic importance of achieving a gross total or near gross total surgical excision[9]. This was, for example, demonstrated in the CCG-921 study, which showed a survival advantage for patients having less than 1.5 cm^2 residual disease on post-operative imaging as compared to those patients with greater or equal to 1.5 cm^2 (see below)[8]. It should be appreciated, however, that in the present era, with modern neurosurgical and neuroimaging techniques, that only a small minority of patients have such so defined significant residual tumour. Presently the COG define standard risk patients in respect of local disease as those having less than or equal to 1.5 cm^2 (maximum cross-sectional area) of residual disease after surgery.

In contrast there was clearly no evidence of a difference in survival between patients with residual disease or no residual disease in the HIT 91 study on which HIT 2000 and thus HIT-SIOP PNET 4 is based. In this respect, for PNET 4, patients with residual disease of any size following surgery are regarded as standard risk patients and are thus eligible for inclusion into the trial. Despite the results from HIT 91, the HIT Group Study Committee do, however, suggest that second look surgery be considered in patients with significant residual disease following primary surgery. This recommendation for second look surgery is stated within the HIT 2000 protocol and is to be continued in the PNET 4 study.

Although the number of patients with significant residual disease is likely to be small, the PNET 4 trial may afford the opportunity to examine further the impact of residual disease following surgery.

Residual disease is best demonstrated by comparing the patient's pre-operative MRI imaging with that obtained post-operatively. It is accepted that postoperative imaging is best performed within 72 hours of surgery, after which post-operative changes render interpretation of residual disease difficult. Therefore for the purposes of this trial all patients should have post-operative imaging within 72 hours. Although post-operative MRI is strongly recommended, CT scan before and after contrast injection is acceptable as postoperative imaging.

4.3 Neurosurgery

The importance of the role of surgical resection in patients with medulloblastoma is widely recognised, although, as discussed above (section 4.2.2), the true prognostic significance of the extent of surgical resection is still unclear.

Neurosurgeons, aided by modern technological adjuncts, make considerable efforts to achieve CR or near CR. Such surgery can bring an increased risk of neurological deficits of a temporary or even a permanent nature. Post-operative complications and neurological deficits resulting from surgery not only impact upon quality of survival but may also contribute to delay in commencing adjuvant therapy. This may be compounded when neurosurgery takes place in one department and the adjuvant therapies are delivered in other departments, or even different institutions. There are, however, few data on the toxicity of surgery and in particular there have been no large prospective studies of the toxicity of surgery in children with PNETs treated according to a set strategy. If the toxicity of neurosurgery is a significant factor then it will be important to identify any causative factors that might be associated with the toxicity lest they be amenable to modification. There have been no previous systematic attempts to define those factors that may predispose towards post-operative complications or new neurological deficits.

Possible factors that might correlate with attempts to achieve CR with surgery, and also with morbidity relate to the patient; the local anatomy; the behaviour of the tumour; the surgical technique, including the availability and employment of high-technology instrumentation; and the surgeon.

A large randomised study of post-operative radiotherapy and chemotherapy provides the ideal setting for addressing these questions, in the context of a trial enrolling a subset of patients with better prognostic features.

As discussed in section 4.2.2, patients with residual disease of any size following surgery are eligible for inclusion into the PNET 4 trial. The Study Committee do, however, suggest that second look surgery be considered in patients with significant residual disease following primary surgery.

In the PNET 4 trial, randomisation will be stratified according to the presence of residual tumour (section 7).

4.4. Radiotherapy in standard risk medulloblastoma.

4.4.1 Rationale for dose reduction.

Until recently, the standard therapeutic approach for standard risk medulloblastoma has consisted of complete or near complete surgical resection followed by post-operative CSRT. The conventional doses of radiotherapy are around 36 Gy to the craniospinal axis together with a boost of 18 to 20 Gy to the posterior fossa (total dose 54 to 56 Gy). Using such doses, various studies have reported that between 55 and 70% of children are alive and free of progressive disease five years from diagnosis[10 11].

It is now clear that a high proportion of survivors of medulloblastoma have significant long-term sequelae. Although some of these late effects are related to the tumour itself, hydrocephalus and the complications of both surgery and chemotherapy, it is probable that the most important factor in the pathogenesis of these significant sequelae is the dose of CSRT needed to treat this disease. Of most concern are the well-recognised neuropsychological sequelae of children receiving cranial irradiation. Several studies have demonstrated marked losses of IQ of up to 30 points or more which are most predominant in young children, particularly those less than seven or eight years of age. Several workers investigating these effects have compared the effects of CSRT for the treatment of medulloblastoma with posterior fossa radiotherapy alone e.g. for tumours such as cerebellar astrocytoma and ependymoma[12]. Such studies have clearly shown the marked deleterious effects of whole brain radiotherapy[13 14].

In addition, it is clear that the majority of survivors suffer significant growth and endocrine dysfunction predominately due to irradiation of the pituitary gland and hypothalamic regions together with the effects of whole spine radiotherapy[15 16 17]. Although exact dose effect relationships are not known, there is evidence to suggest that dose reduction might decrease the risk for such hypothalamic-pituitary dysfunctions as well as for decreasing the risk for growth retardation of the spine. Moreover, radiotherapy of the spinal canal may be responsible for thyroid dysfunction, and also gonadal dysfunction in young girls caused by scattered irradiation.

Several, often small, studies do appear to show a dose effect relationship between 24 and 36 Gy to the brain[18 19 20] although such studies usually contain small numbers and/or a heterogeneous population in terms of disease and treatment. In a recent study, Grill et al showed there is a significant correlation between the full-scale IQ score (FSIQ) and the CSRT dose, with mean FSIQ scores at 84.5, 76.9 and 63.7 for 0 Gy (i.e. posterior fossa radiotherapy alone), 25 Gy and 35 Gy of CSRT respectively[21]. An analysis of the neuropsychological sequelae reported in the literature[22] has been used to construct a dose response curve, which relates to the probability of neuropsychological sequelae to the brain RT dose. This pooling of data suggests a dose response effect with greater morbidity seen with increasing cranial RT dose. There has only been one study that attempted to examine this dose effect in the context of a randomised control trial. Mulhern examined the neuropsychological functioning of survivors of children with medulloblastoma entered into the POG 8631/CCG 923 study described below[23]. This showed that children treated with 23.4 Gy CSRT experience less neuropsychological toxicity than those treated with 36 Gy CSRT. However, the number of patients studied was small, the individual patients IQ changes varied considerably and the results of this cross sectional analysis were not confirmed on a longitudinal basis.

In the recently completed CCG 9892 study, the neuropsychological effect of 23.4 Gy CSRT was reported to be a decline of 4.3 Full Scale IQ points per year[24]. The median interval between radiotherapy and the patient's most recent evaluation in that study was 2.5 years. The declines in IQ were reported to be relatively more marked in females, children with higher baseline scores and children aged less than 7 years. The authors considered that their findings were suggestive of some degree of intellectual preservation compared to the effect of conventionally dosed radiotherapy but also stated that the estimated IQ drop of 20.8 points in their younger group did not clearly support an advantage to these patients for the reduced radiotherapy regimen.

With regard to the survival outcome of patients receiving reduced dose radiotherapy following surgery, pilot data suggested the feasibility of this approach in patients with non-metastatic disease and who underwent gross total resection. Attempts have been made to control tumour growth and to decrease the long-term neurocognitive effects of radiation, especially in young children by reducing the dose given to the brain and spine[25 26 27 28 29 30 31]. In a non-randomised single arm study of adults and children with medulloblastoma 77 % of the patients who received 24 Gy to the craniospinal axis and 54 Gy to the primary site survived free of disease for five years [28].

The SIOP II trial randomised standard risk patients between four arms (low dose [25 Gy] CSRT vs standard dose [35 Gy] CSRT and two arms with randomisation for the addition or not of chemotherapy). The arm with chemotherapy and low dose radiation therapy exhibited the worst survival rate. The arm with low dose without chemotherapy had an event free survival of 67 %, which was equivalent to that seen in those patients receiving the standard dose of craniospinal radiotherapy [32]. However, analysis of this data must be considered carefully because of :

- Relatively low numbers in each arm of the study.
- An heterogeneity between the prognostic subgroups (most of the children did not have spinal imaging – myelography).
- Radiation therapy technique was heterogeneous between the different centers.
- The rate of failures in the posterior fossa occurred more frequently as compared to other studies, the high incidence of which could not be attributed to dose reduction since most of children received 55 Gy to the posterior fossa.

In the North American POG 8631/CCG 923 study, standard risk medulloblastoma children were randomised to a CSRT dose of either 36 or 23.4 Gy without chemotherapy in either arm[33 34]. This study was opened in 1986 and accrued 98 eligible patients prior to its premature closure in 1990 when an excess of relapses was observed in the reduced dose arm. Although no significant difference is observed, long-term follow-up confirmed the original one-sided conclusions with a 67% EFS at 5 y for patients treated with a standard dose neuraxis irradiation and 52% for those treated with a reduced dose (p=0.08). At eight years, the respective EFS were also 67% and 52% (p=0.141).
Following the early closure of POG 8631/CCG 923 with the observed increased risk of leptomeningeal relapse, investigators in the US continue to explore the use of reduced dose CSRT, but with the administration of chemotherapy following RT. Following encouraging data from pilot studies, Packer and co-workers investigated the use of reduced dose CRST of 23.4 Gy with a boost of 31.8 Gy (total posterior fossa dose 55.2 Gy) followed by chemotherapy in carefully staged 'standard risk patients'. The chemotherapy regimen consists of three drugs, Vincristine, CCNU and Cisplatin. Eight doses of Vincristine were given during RT. Six weeks after the end of RT, patients were started on a regimen of cycles of all three drugs given every six weeks. Eight six-week cycles of chemotherapy were planned, but the protocol included modifications based on toxicity, in particular ototoxicity due to Cisplatin.

The results of this limited centre study, CCG-9892, were reported in 1999[35]. Progression free survival (PFS) of the 65 children entered was 86% +/– 4% at 3 years and 79% +/– 7% at 5 years. Sites of relapse for the 14 patients who developed progressive disease included the local tumour site alone in two patients, local and disseminated disease in nine and no primary sites in three. Treatment was relatively well tolerated, although it is of some concern that the dose of Cisplatin had to be modified in more than half the patients and at follow up 32% of patients had grade 3 or 4 ototoxicity[36]**.** These results are the best published results for standard risk patients. Some caution, however, must be attached to the results of this non-randomised study as the number of patients is relatively small and the number of centres limited and that this regimen has not yet been tested in the context of a large group-wide multicentre randomised study. Nevertheless, these results have generally been accepted as very encouraging and strongly suggest (e.g. by comparison with POG 8631/CCG 923) a role for post-RT chemotherapy in the context of reduced dose RT. The CCG-9892 study treatment regimen has been carried forward as the standard arm of the recently closed CCG/POG study, A9961 (opened 1998) which compared in a randomised fashion two post-RT chemotherapy regimens; CCNU, Cisplatin and Vincristine and Cyclophosphamide Cisplatin and Vincristine. As well as answering the randomised question, this study that has accrued over 400 patients, should address the reservations attached to the results of CCG 9892 discussed above. The SIOP Brain Tumour Committee have also been very encouraged by the results of CCG 9892 and the results of this study together with a desire to further investigate reduced-dose RT have led to reduced dose radiotherapy followed by a 'Packer chemotherapy' being included as the standard arm in the present study.

4.4.2 Rationale for Hyperfractionated radiotherapy

Conventional fractionation in radiotherapy has evolved empirically and generally involves giving one fraction per day, five days per week on Mondays to Fridays. In paediatric radiotherapy practice, the daily dose per fraction is generally between 1.5 and 2.0 Gy. In the case of conventionally fractionated radiotherapy for medulloblastoma, such as in the current North American COG studies, the dose per fraction is generally 1.8 Gy.

In selecting the total dose of radiotherapy to be delivered to a tumour the aim is to achieve the maximum tumour control with acceptable long-term morbidity. For CNS tumours the important dose limiting tissue is the CNS. Exceeding this tolerance dose carries an increased risk of severe late morbidity such as radiation necrosis[37]. This limits the dose of radiotherapy that can be delivered to CNS tumours.

Over the last three decades there have been a number of attempts to compare different regimens of radiotherapy dose and dose per fraction with the development of 'isoeffect formulae'. For the last 10-15 years it has been accepted that for a given tissue and a given effect in this tissue the shape of the radiation dose–effect curve which most accurately fits in vitro, in vivo and clinical data can be described by the 'Linear Quadratic Model'[38]. This model describes the relationship between dose and response for various dose/fractionation regimens. According to the linear quadratic model, effect = $n(\alpha d + \beta d^2)$ when n is the number of fractions and d is the dose per fraction (Gy). The α and β exponents in the equation are specific for the tumour or tissue in question. The α exponent refers to the linear (single track) component of cell killing while the β exponent refers to the quadratic (double track) component of cell killing. The α/β ratio determines the degree of 'bendiness' of the cell survival curve. Figure 1 illustrates the relationship between α, β and the α/β ratio for a typical cell survival curve.

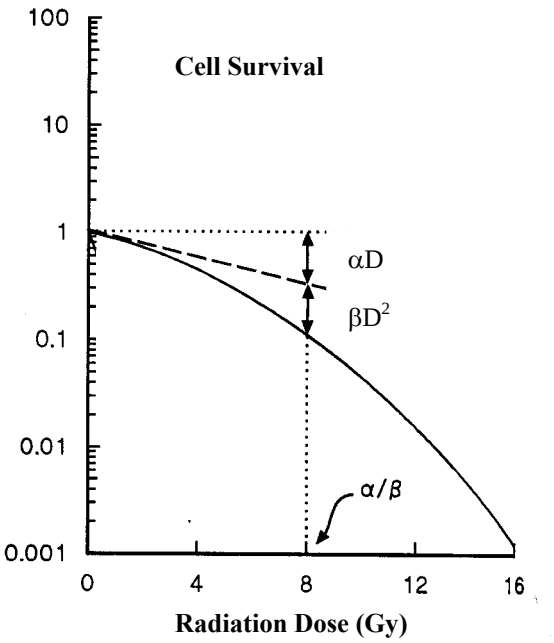


Figure 1 - Alpha/Beta Ratio for Cell Survival Curve

Early reacting tissues that include mucosa, bone marrow, and most tumours have a higher α/β ratio (typically $\alpha/\beta = 10$). Late reacting tissues including the CNS, lung and kidney have a small α/β ratio (for CNS, $\alpha/\beta = 2$) and a dose response curve rapidly curving in the region of radiotherapy dose per fraction commonly employed in clinical radiotherapy. This type of tissue demonstrates a critical dependence on the fraction size. For 'early reacting tissues' and tumours the dose response curve is therefore less curved than that for late reacting tissues such as the CNS. As a consequence there is less dependence on fraction size[39]. This means that by decreasing the size of fraction from 1.8 Gy (conventional fraction size) to 1 Gy (as in the proposed HFRT regimen) the effects in 'late reacting tissues' ($\alpha/\beta = 2$ assumed for CNS) are predominantly spared in comparison to effects in early reacting tissues and tumours ($\alpha/\beta = 10$).

HFRT involves giving a smaller dose per fraction, with radiotherapy fractions administered at least twice each day. The total radiotherapy dose is increased and the total duration of treatment remains approximately the same. Small doses given more than once a day, usually 6 to 8 hours apart, produce a redistribution of proliferating tumour cells with some cells entering a radiosensitive stage. Other non-proliferating or dose-limiting tissue, such as normal brain, will potentially be spared this effect of redistribution. HFRT exploits the differences in repair capacity between tumour and late responding normal tissues such as the CNS. Thus the aim of hyperfractionation is to improve the therapeutic ratio, either by enhancing the anti-tumour effect, without an increase in late effects, or by maintaining the same level of anti-tumour effect and reducing late morbidity. In order to maintain an iso-effect in tissues, due to the sparing effect of smaller fractions (of which molecular mechanism are still hypothetical), the total dose has to be increased. Dose/fractionation regimens can be compared by the following equation:

n1 ($\alpha d1 + \beta d1^2$) = n2 ($\alpha d2 + \beta d2^2$) from which is derived:

'New total dose' (D2) / 'Old total dose' (D1) = n2 x d2 / n1 x d1 = (α/β + d1) / (α/β +d2)

$$\mathbf{D2 = \frac{D1 \times (\alpha/\beta + d1)}{(\alpha/\beta + d2)}}$$

Using this formula the dose equivalents for a hyperfractionated regimen can be compared with a conventionally fractionated regimen as given in table 1.

The doses of radiotherapy for each arm in PNET 4 are as follows:

HFRT (experimental arm)

Craniospinal axis: 36Gy in 36 b.d. fractions of 1 Gy

Post fossa: 60 Gy in 60 b.d. fractions of 1 Gy

Tumour bed: 68 Gy in 68 b.d. fractions of 1 Gy

Conventionally fractionated RT (standard arm)

Craniospinal axis: 23.4 Gy in 13 daily fractions of 1.8 Gy

Post fossa: 54 Gy in 31 fractions of 1.8 Gy

Table 1.

Equivalent doses (at 1.8 Gy per fraction) for HFRT in PNET-4

		CNS Late effects Equivalent Dose	Anti-tumour effect Equivalent Dose
		$\alpha/\beta = 2$	$\alpha/\beta = 10$
CSRT	36 Gy 36 fractions	28.42	33.56
Post Fossa	60 Gy 60 fractions	47.37	55.93
Tumour bed	68 Gy 68 fractions	53.68	63.39

Thus hyperfractionation has the potential for preferentially increasing the anti-tumour effect without an equivalent increase in CNS late effects.
The dose-response relationship for medulloblastoma is well known and it seems that increasing the dose without increasing the late effects on CNS tissue might additionally improve local and regional tumour control [28 40 41 42].

Clinical pilot studies of HFRT

Allen et al, 1996[40]
Following surgery, 23 patients with 'high stage' PNET were treated between 1989 and 1995 with CSRT 36 Gy in 1 Gy b.d. fractions, followed by a further 36 Gy in 1 Gy b.d. to the posterior fossa giving a total dose to the posterior fossa of 72 Gy in 72 fractions. This was followed by adjuvant chemotherapy for a total of nine months. Of 15 patients with non-metastatic medulloblastoma, 14 were in continuous CR at a median follow-up of 78 months. The one patient who relapsed in this group had a solitary spinal relapse. Patients with metastases and with non-cerebellar primaries did less well.

Prados et al, 1999[42].
This was a study of HFRT for patients with PNET, including 25 with medulloblastoma, 5 with pineoblastoma, 5 cerebral PNET, 1 spinal cord PNET and 3 malignant ependymoma. The RT dose was given in 1 Gy b.d. fractions. The CSRT dose was 30 Gy and the posterior fossa dose was 72 Gy. Patients with 'standard risk' disease received RT only and those with 'high risk' disease received post-RT adjuvant chemotherapy with 'Packer' chemotherapy (cisplatin, vincristine, CCNU). Three year PFS for 16 'standard' risk patients with medulloblastoma was 63%, and 56% for 9 with high-risk disease. For the total of 25 patients with medulloblastoma, there were only two relapses in the posterior fossa, one of which was solitary. The majority of relapses occurred outside the posterior fossa. The results of this study suggest that a CSRT dose of 30 Gy given in a 1 Gy b.d. dose without chemotherapy is inadequate to control spinal disease.

Marymont et al, 1996[41]
Between 1986 and 1991, 13 'high risk' patients, 11 with medulloblastoma and 2 with supratentorial PNET, were treated with a variety of HFRT and chemotherapy regimens in a pilot feasibility study. Of the 11 patients who had residual disease in the posterior fossa or M3 disease, 7 (64%) had not recurred with a follow-up time of 10 to 96 months (median 53). This small study suggested that HFRT to the craniospinal axis was feasible.

AIEOP Studies
A study of HFRT has been carried out by AIEOP (SNC91 protocol). The CSRT dose was 30-36 Gy in 1 Gy bid fractions, followed by a boost to the posterior fossa up to a total dose of 66 Gy. All patients were given chemotherapy, both before and after CSRT. Preliminary data reported by Ricardi[43] on 23 patients clearly showed that 30 Gy given by b.d. fractionation is not sufficient in preventing leptomeningeal spinal relapses, even in standard risk medulloblastoma and with chemotherapy (see Table 2).

The current Italian protocol in standard risk medulloblastoma (AIEOP SNC99) is still employing HFRT, with 36 Gy CSRT and 66 Gy to the posterior fossa in 1 Gy b.d. fractions. Recruitment is good and the increasing numbers of radiotherapy centres are able to comply with the HFRT regimen.

From the AIEOP studies, there is clinical data that suggests a possible sparing effect of hyperfractionation in terms of preservation of thyroid function[43 44].

The outcome from the clinical pilot studies of hyperfractionated radiotherapy is given in table 2.

Table 2

Outcome from pilot studies of hyperfractionated radiation therapy for medulloblastoma and supratentorial primitive neuroectodermal tumours.

Author	Patients	Therapy	Relapse-free Survival	Follow-up. (months)
Prados[45]	23 'low risk' 16 'high risk'	24-30 Gy / 72 Gy 30 Gy / 72 Gy + Chemo.	79% 69%	23 (> 70)
Halperin[46]	5 - PNET 1 – Biopsy Only 4 – Complete resection.	30.6 – 43.9 Gy / 50 – 63.7 Gy + Chemo.	4 of 5 Alive in CR. 1 Alive with stable disease (2,3 years)	52 – 96
Allen[40]	15 'high risk' (M0) 4 MB – M2/3 4 PNET- M2/M3	36 Gy / 72 Gy + Chemo.	93% 50% 0%	75 35-67
Marymont[41]	11 'high risk' (M2/3)	34 Gy /72 Gy + Chemo.	64%	53
*Prados[42]	16 'low risk' 9 'high risk' 11 PNET	30 Gy / 72 Gy 30 Gy / 72 Gy + Chemo. 30 Gy / 72 Gy +/- Chemo.	63% 60% 7 relapses (5 local)	7-88 8-56 14-66
Ricardi[43]	Group 1 7 pts Group 2 16 pts	30/66/30 Gy (for standard risk) 36/66/30 (for standard risk)	14% (5 early isolated spinal relapses) 76%	84-108 36-84

*In part this was an up-date of Prados, 1994

4.4.3 Rationale for the reduced target volume after 60 Gy to the posterior fossa in the HFRT arm

Traditionally the primary tumour 'boost' has been delivered to the entire posterior fossa. However, this involves a significant dose of radiotherapy to areas of the cerebral cortex adjacent to the cerebellum, which may contribute to the long-term neuropsychological sequelae. It is not clear that the 'boost' needs to be delivered to the entire posterior fossa. In a pattern of relapse study by Fukunaga-Johnson et al, 114 patients were treated with a 'boost' to the entire posterior fossa. Of the 27 patients who had a recurrence, 14 had a tumour recurrence within the tumour bed, 11 also failed in the spine and 8 in the meninges of the posterior fossa but outside the tumour bed[47]. Local failure within the posterior fossa but outside the tumour bed as any component of first recurrence occurred in 41% (11 of 27) of all

failures, but as the solitary site of first failure in only 1 of 27 failures. In order to attempt to reduce the long-term effects of the RT to the posterior fossa, patients in the HFRT arm of PNET 4 will have a dose reduction after 60 Gy. It is hoped that HFRT will allow a reduction in long-term effects while maintaining the same level of anti-tumour effect on the meninges of the posterior fossa compared with the radiotherapy regimen in the conventionally fractionated arm. For the final phase of radiotherapy in the HFRT arm, a dose of 8 Gy will be delivered to the tumour bed with conformal planning. This should involve an escalation of the anti-tumour effect on the tumour bed that has been the predominant site of relapse in some recent studies such as the HIT 91 study[48].

The equivalent doses at 2 Gy per fraction for conventionally fractionated and HFRT regimens are given in table 3.

Table 3.

A comparison between conventionally fractionated and hyperfractionated radiotherapy on the effective doses to tumour and normal neural tissue.

	EQUIVALENT DOSE (Gy) (measured against 2 Gy per fraction)						
	Prescribed Dose		Dose/ Fraction	$\alpha/\beta = 10$ Early tumour effects		$\alpha/\beta = 2$ Late effects	
	PF	CSRT		PF	CSRT	PF	CSRT
Standard[49]	54	36	1.8 x 1	52.2	34.8	48.9	33.9
M-SFOP 93[50]	54	25	1.8 x 1	52.2	24.2	48.9	23.3
Allen[40]	72	36	1 x 2	66	33	54	27
M-SFOP 98[51]	68	36	1 x 2	62	33	51	27
AIEOP-MB99[52]	66	36	1 x 2	60	33	49	27
Packer[35]	55.8	23.4	1.8 x 1	53.4	23.1	51.2	22.2

PF = Posterior Fossa

4.5 Role of chemotherapy in standard risk medulloblastoma

Medulloblastoma is clearly a chemosensitive tumour, as demonstrated in numerous phase II studies for relapse[53 54 55 56 57] or in the initial treatment of metastatic disease[58 59].

Over the last 25 years, a number of multicentre studies have addressed the role of adjuvant chemotherapy in order to improve survival in medulloblastoma and, more recently, to facilitate a

reduction in the dose of CSRT. The North American CCG-942 (1976-1981) study compared RT alone (craniospinal dose 35-40 Gy) with RT followed by chemotherapy (Vincristine, CCNU, and Prednisolone). Overall, for the 223 children entered into the study, five year progression free survival (PFS) was 55%[60]. Although there was no statistical difference in survival between the two treatment groups, in the group of patients with high stage disease, those children randomised to receive post-RT chemotherapy had a PFS of 46% and an overall survival (OS) of 57% as compared to those treated with RT alone who had a PFS of zero and OS of 19%.

The SIOP 1 study was similar in design and ran between 1975 and 1980. 286 patients were randomised to RT alone (CRST dose 30-35 Gy) or RT plus chemotherapy with CCNU and Vincristine. As with the CCG 942 study, there was no significant difference in survival between the two groups but a benefit for chemotherapy in terms of improved survival was noted for a subgroup of patients who had metastatic disease, subtotal resection, brain stem invasion and Chang Stage T3 and T4 disease[49]. In summary, both these first generation randomised studies, as well as non-randomised studies[26 61 62 63], suggested a benefit for chemotherapy given after radiotherapy in patients with high-risk features.

The next generation of studies focused on the investigation of the timing of chemotherapy, particularly the use of pre-RT chemotherapy or so called 'sandwich chemotherapy'. In the SIOP 2 study described above, no benefit was seen for sandwich chemotherapy prior to 35 Gy CRST and a decrease in survival was seen for patients treated with chemotherapy before reduced dose CRST of 25 Gy[32].

The most recent SIOP study (PNET 3) ran between 1992 and 2000. Patients were randomised to receive immediate radiotherapy alone or 'sandwich chemotherapy' consisting of a twelve-week regimen of four pulses of chemotherapy, two courses each of Carboplatin and Etoposide alternating with Cyclophosphamide and Etoposide. The radiotherapy dose was 35 Gy CSRT, which was based on the early results from SIOP 2 that suggested an overall benefit for conventional as opposed to reduced dose radiotherapy. This trial was compromised by a low accrual rate and over the nine years of the study, only 179 patients with standard risk medulloblastoma were randomised. Preliminary results suggest the benefit of chemotherapy[64]. A significant difference in EFS was demonstrated for patients treated by chemotherapy and RT at 3 and 5 years with an EFS of 78.7% and 73.4% respectively compared with 64.2% and 60.0% for RT alone (p=0.0419). The 3-year and 5-year OS for the two arms were 82.1% and 76.1% for patients treated with chemotherapy and RT, compared with 75.8% and 66.5% for treatment with RT alone (p = 0.1662). For patients who had undergone a total resection event-free survival was significantly better with chemotherapy + RT than RT alone (p=0.0346).

Due to the widespread acceptance of the role of chemotherapy in both standard and high risk medulloblastoma the PNET 3 study was probably the last in which adjuvant chemotherapy will be tested against radiotherapy alone.

Further randomised studies have compared pre-RT with post-RT chemotherapy. The North American CCG 921 study compared chemotherapy with the so called 8-in-1 regimen given for two courses, pre-RT and for 8 courses after RT with a standard chemotherapy arm consisting of post-radiation chemotherapy with Vincristine, CCNU and Prednisolone (VCP)[8]. The radiotherapy dose to the craniospinal axis was 36 Gy and dose to the posterior fossa 54 Gy. Although the study was designed for so called high risk patients, the risk categorisation differed from that used today in that patients were included on the basis of more extensive local disease at presentation according to Chang staging system. This and other studies subsequently showed that the amount of the residual disease after

surgery, rather than the pre-operative extent of disease, carries most prognostic significance in terms of local disease. The OS and PFS rates were 55 and 54% respectively at a median follow up of seven years. Patients treated using the control arm had improved survival as compared to those on the experimental arm (PFS 63% v 45%). Among the medulloblastoma patients, both the presence and extent of metastatic disease was shown to be prognostic determinant with progression free survival for M0, M1 and M2+ of 70%, 57% and 40% respectively. As discussed above, the degree of residual disease following surgery was also found to be of prognostic importance. Patients having less than 1.5 cm^2 had a PFS at five years of 76% as compared to those patients with greater or equal to 1.5 cm^2 of 54%. In contrast, the degree of surgical resection, as determined by the percentage of tumour removed, was not in itself found to be an independent prognostic factor.

The German HIT 91 Study compared in children aged more than three years, 'sandwich chemotherapy' with Ifosfamide, Cisplatin, Methotrexate, Etoposide and Cytarabine with immediate radiotherapy followed by maintenance chemotherapy with the Packer regimen of CCNU, Vincristine and Cisplatin[48]. The CSRT dose was 35.2 Gy and the posterior fossa dose 55.2 Gy. There was an advantage for the maintenance post-RT chemotherapy as compared to the sandwich chemotherapy arm with relapse free survival of 78 versus 65% at three years for non-metastatic patients. The excellent survival of children in the immediate radiotherapy arm of HIT 91 provides additional evidence of the benefit of post-RT chemotherapy using the Packer regimen as well as that described by Packer himself when the chemotherapy is used following reduced dose radiotherapy. A further North American Study, POG 9031, has again investigated the timing of chemotherapy with preliminary reports suggesting no increased survival for children given one course of chemotherapy delivered before RT and one course after RT as compared to those patients given both courses of identical chemotherapy after RT[65]. Despite the initial enthusiasm for 'sandwich chemotherapy', no study to date has shown a benefit for this approach as compared to post-radiation chemotherapy. In addition, studies such as SIOP 2[32] show a possible detrimental effect of delaying radiotherapy, and it is now widely accepted that an important part of the management of standard risk medulloblastoma is to deliver radiotherapy without delay.

4.6 Biological studies

Despite the identification of oncogenes and tumour suppressor genes important in the progression of a variety of human cancers, including some brain tumours, relatively little is known about the molecular pathology of CNS PNETs. In particular, though a number of consistent karyotype abnormalities has been identified in PNETs, as has a small group of candidate oncogenes and tumour suppressor genes, an understanding of their biological / clinical significance is limited. The biological studies attached to PNET 4 will investigate the prognostic significance and other clinical associations of several molecular abnormalities previously identified in smaller more heterogeneous cohorts of PNET patients. In particular, they will investigate any relationship between specific molecular abnormalities and treatment response and clinical outcome, with the principal aim of identifying valuable prognostic markers for a more efficient patient stratification in future SIOP clinical trials. Furthermore, by recording the frequency and distribution pattern of these aberrations, both with regard to each other and other clinicopathological features, it is hoped that considerable insight will be gained into our understanding of PNET tumour biology. Finally, an important principle of the study is to demonstrate that collaborative research can be undertaken in the context of a SIOP trial across several countries in Europe.

4.6.1 Abnormalities of chromosome 17 and loss of 9q22

Deletions involving the short arm of chromosome 17 represent the most frequent genetic abnormality in medulloblastoma, occurring in 40 to 50% of primary tumours[66]. Though a number of studies in the literature have reported a significantly worse prognosis for patients whose tumours harbour deletions of 17p[67 68] this has not been a universal finding[69 70]. However, these studies have involved only small numbers of cases or combined a variety of techniques with different sensitivities to analyse 17p loss, thereby rendering them difficult to interpret. Loss of 17p is associated with gain of 17q, consistent with an isochromosome 17q i(17q), in a large proportion of medulloblastomas.

There is increasing evidence that the human homologue of *Drosophila* segment polarity gene *patched (PTCH)* may act as a tumour suppressor in medulloblastoma. The possibility that deregulation of this system may result in malignant proliferation of granule cells and tumorigenesis was first suggested by the discovery that *PTCH* function is lost in Gorlin syndrome (GS), an inherited disorder associated with an increased risk of tumour development including medulloblastoma[71]. Following the localisation of the GS locus to 9q22.3-q31, two LOH studies identified deletion of this region not only in medulloblastomas derived from GS patients, but also in 5 of 33 sporadic tumours[72 73]. The gene responsible for GS was subsequently cloned and identified as *PTCH*[74]. Direct sequence analyses have since detected mutations in the *PTCH* gene in 12 out of a total of 97 sporadic medulloblastomas[75 76], and a close correlation between LOH at 9q22-q23, mutation of *PTCH* and the desmoplastic morphophenotype has been demonstrated[75].

Using an interphase FISH method on tumour nuclei extracted from paraffin wax embedded tissue[77], this study will test the hypotheses that loss of 17p, gain of 17q, i(17q) or a combination of these abnormalities is a prognostic marker for childhood PNETs and that loss of 9q22 is associated with a particular morphophenotype and biological behaviour.

4.6.2 ErbB receptor expression

In medulloblastoma, there appears to be a close relationship between the proportion of cells with elevated expression of ErbB2 and ErbB4 and high tumour mitotic index, advanced metastatic stage and reduced survival[78]**.** Using immunohistochemistry, this study will test the hypothesis that PNETs with a majority of ErbB2-positive cells demonstrate a more aggressive biological behaviour.

4.6.3 *MYC* oncogene amplification

Available data suggest that around 6% of primary medulloblastomas harbour amplification of the *MYC* oncogene. Several studies have reported an adverse affect of *MYC* amplification on clinical outcome[67 79]. Further, evidence of an association between aggressive tumour behaviour and *MYC* amplification has been provided by Scheurlen *et al* [80]**,** who reported a *MYC* amplification rate almost three times that observed in other studies (17%, n=5/29) in an analysis which included samples from clinically high risk patients. This study will examine *MYC* status using a combination of interphase FISH and qPCR.

4.6.4 Expression of TrkC and *MYC*

The family of neurotrophins have pleiotrophic effects on developing, mature and injured cells of the CNS[81]. Recently, two groups[82 83] have found that TrkC mRNA expression is an independent predictor of a favourable clinical outcome in PNET patients in retrospective studies. By combining high TrkC mRNA expression and low MYC mRNA expression, the predictive power to identify a good-outcome group of medulloblastoma patients has been shown to be even greater[84]. Utilizing

quantitative RT-PCR, this study will prospectively analyse TrkC mRNA and MYC expression in the trial's patients.

4.7 Systematic evaluation of health status, behaviour, perceived quality of life, endocrine function and hearing

4.7.1. What determines quality of survival?

The quality of survival of children is a dominant issue in the management of children receiving treatment for most types of brain tumours. With medulloblastoma, numerous studies have documented poor outcomes. The effects of radiotherapy and of chemotherapy are widely recognised to be relevant to the adverse neurological, neuropsychological and endocrine outcomes following treatment for this condition. Arguably, however, these treatments may be no more important as determinants of outcome than the tumour itself, peri-operative morbidity, and psychosocial adversity, the 'dose' and timing of which are more difficult to measure.

4.7.2 Value of a prospective study

The apparent cognitive advantage in children treated with lower doses of cranial irradiation has only been documented in cross-sectional studies of an incomplete, and possibly self-selecting, sample of treated children whose follow-up was short. In these studies, the benefit of reduced dose radiation has not been confirmed from longitudinal data[23 24]. Measurement of quality of survival is integral to the design of the present study. The collected information will, for the first time, provide a brief but wide-ranging longitudinal set of information describing the evolving outcomes in these children.

4.7.3 Methodology

In order to achieve the numbers required for the necessary power to draw reliable conclusions, the methods used to collect outcome data need to be applicable in multiple centres. Comparison of short questionnaires with more in-depth measures suggests that remarkably similar information can be gleaned by the two methods in children with medulloblastoma[85]**.** The aim is to express outcome in a standardised framework that includes the full range of types of difficulties and disabilities considered relevant by families: this will document health status, behaviour, endocrine and audiological function, and the subjective experience of the child and family. This framework is a modification of the assessment proposed by Glaser *et al* in 1999[86]**.**

The proposal is thus to assess longitudinally various aspects of health status and quality of life in survivors on five occasions (post surgery/before RT, at the end of treatment, three and five years after diagnosis and again at 20 years of age) using several brief questionnaires. These will be completed by parents for all patients and also by patients themselves if aged 11 years or more. Information about health status prior to illness will also be sought. For growth and other endocrine outcomes, objective measurements obtained at least annually by specifically trained health care staff according to standard published criteria[87 88] are usually necessary for interpretation of the findings. The over-riding concern is to keep assessments short and simple. The rationale for choice of, and timetable of, measurements is described in Appendix M and, briefly, below.

4.7.3.1 Cross Sectional Data Collection

An additional cross sectional data collection point will be conducted starting in October 2010 to obtain a snap-shot of quality of survival data. It has been necessary to implement the collection of an additional set-of data because the quality of the data obtained so far from the longnitudial study has been poor and unanalysable. The question of quality of survival has

become even more crucial, as the emerging data suggests that there is no significant difference in event free survival between the treatment arms (Lannering, B., Rutowski, S., Doz, F., Pizer, B, Gustafsson, G., Navajas, A et al. (2010). HIT-SIOP PNET 4 – A randomised muticentre study of hyperfractaionated (HFRT) versus standard radiotherapy (STRT) in children with standard risk medulloblastoma. *Neuro-oncology*, *12*, ii5). The information obtained from the cross-section data collection will help to inform the upcoming PNET 5 and PNET 6 studies.

The assessments used in the cross-sectional data collection are listed in Appendix M.

4.7.4 Health status and behaviour

The Health Utilities Index (HUI)[89] is a 15 item plus one 'global' question, wide ranging measure of health status, which allows comparison of global Health Status or of the 'attributes' of vision, hearing, speech, dexterity, ambulation, cognition, emotion, and pain. This has been found to be sensitive to clinical problems (excepting behavioural problems) in populations of children who have been treated for brain tumours (referenced in Kennedy and Leyland, 1999[90]) including medulloblastoma[91]. The Strengths and Difficulties Questionnaire (SDQ)[92] is a 25-item questionnaire with subscales for hyperactivity, emotional symptoms, conduct problems, peer relationships, and prosocial behaviour. These problems are very prevalent among children with brain tumours[90]. Both the HUI and the SDQ are available in many European languages and will provide a concise description of the health status and behaviour of children enrolled in the trial. They are the core outcome measures of this aspect of PNET 4.

4.7.5 Endocrine function

Between 60 and 95% of children with brain tumours experience hormonal deficits, particularly growth hormone insufficiency, within 2-5 years of treatment[93 94] and hormone status has important effects on QoL, as exemplified by the need for adult hormone replacement therapy.

Central Hypopituitarism. Dose- and fractionation-dependent neurotoxic effects of cranial irradiation have been blamed for the evolving hierarchical loss of post-operatively intact anterior pituitary hormones[95] but the contribution of chemotherapy or surgically induced late neural damage has generally not been considered significant. The few prospective and longitudinal studies of children with tumours in the posterior fossa, distant from the pituitary axis, have shown subtle neuroregulatory deficits in growth hormone (GH) secretion, which exist even before irradiation, and are compounded by it. Chemotherapy is additively toxic, progressively disrupting central GH release mechanisms and thereby confusing the interpretation of various dynamic GH provocation tests[96]

Peripheral target organ effects. The aetiology of short stature in children treated for medulloblastoma is further confounded by irradiation-induced skeletal spinal damage[97] and an early puberty[93] limiting the time for growth despite GH replacement. With older spinal irradiation techniques, subfertility and hypothyroidism, potentially compromising future reproductive and skeletal health, affected approximately one third of survivors, this figure increasing in one study, to approximately two-thirds due to the added toxicity of chemotherapy[94 98]. These figures may increase, particularly in females, as more survivors achieve adulthood and/or their increasing longevity unmasks a premature menopause.

Data to be collected: Height, sitting height, weight, pubertal stage and serum concentrations of thyroxine, thyrotropin (TSH), gonadotrophins and sex steroids will be measured at the same 5 time points as other outcome data, including investigation at adult height (aged 20). Measurement of gonadotrophins and sex steroids will be restricted to those children aged eight years or more. Serum measurements of both central (pituitary) and end-organ (target gland) hormones are required to determine the central/peripheral drive/response components of endocrine dysfunction especially because of the possible of an increased gonadal toxicity with hyperfractionation. Age at onset of puberty (calculated retrospectively from annual examination) and at menarche, use of supplemental hormone therapy, birthweight, gestational age at birth, and parental heights will be recorded.

4.7.6 Audiology

High frequency hearing loss progressing to involve the speech frequency range (500-3,000 Hz) is a

major toxicity of cisplatin. It is clear that the ototoxicity is dependent upon the cumulative dose of cisplatin, but other factors such as the dose per course and drug scheduling may be important. This effect is compounded by the effect of young age, the tumour itself, preceding cranial irradiation and dark eye colour[36 99]. Of the 65 patients treated in CCG 9892, 21 (32.3 %) developed Grade 3 or 4 ototoxicity[35]. In these patients, hearing loss occurred as early as the third cycle of CCNU, cisplatin, vincristine chemotherapy and as late as the seventh cycle. Ototoxicity was the principal reason for dose modification or curtailment of chemotherapy. By contrast, Grade 3 or 4 ototoxicity occurred in only 11 % of patients with medulloblastoma treated on the maintenance arm of the HIT 91 study, despite similar chemotherapy[48]. The difference between the incidence of ototoxity noted in CCG 9892 and HIT 91 probably mainly reflects the difference in Cisplatin dose modification criteria used in these two studies.

Monitoring of hearing loss is a fundamental and mandatory part of this study. In PNET 4, the ototoxicity grading system devised for both HIT 91 and HIT 2000 will be used. Similarly, dose modification in PNET 4 will be that used in these two HIT Group studies. It is thus anticipated that ototoxicity associated with PNET 4 be significantly less than that reported from studies using Cisplatin containing maintenance therapy performed by the COG Group and elsewhere.

It is, however, appreciated that it is important to compare accurately the ototoxity following treatment according to the PNET 4 trial with other studies in which the the Brock/CTC grading system[100] ototoxity is generally used. In this respect, it is mandatory for patients entered into PNET 4 to have a pure tone audiogram performed at the end of treatment. Hearing loss at this time will be graded according to the Brock/CTC system and recorded either on the study Data Forms or, in the case of HIT Group patients, a hard copy of the audiogram will be sent the HIT Group National Data Centre.

Data to be collected: Pure tone audiometry (PTA) will be undertaken before therapy and before every subsequent course of chemotherapy and graded according to the HIT scoring system (section 10.4.4). Chemotherapy will be modified on the basis of ototoxicity (section 10.4.4). Audiology will also be monitored as a late effect of treatment (section 10.4.4 and table in section 1.5) with the audiogram at end of treatment being graded according to the Brock/CTC system as described above.

4.7.7 Perception of health and well being

i) Optional measures according to decisions of national groups

Parents' and patients' subjective perception of their health and well being, referred to as 'quality of life' (QoL) measures, provides important information. Recent studies in German children treated for brain tumours[101] reported correlations between, on the one hand, late effects, psychosocial and behavioural problems and, on the other hand, the patients self-perception of QoL[102]. QoL evaluations will be measured by selected comparable brief questionnaires that are age-specific and at least one of which is applicable to most European languages. These are: the PedsQL (Pediatric Quality of Life Inventory)[103], the PEDQOL (Pediatric Quality of Life Questionnaire)[101] and the CHQ-PF28 (Child Health Questionnaire, parent form)[104].

ii) Mandatory measures

The EORTC QLQ-C30 questionnaire[105] including a module specifically designed for adults with brain

tumours, may be used in all patients aged 17 years or more but is mandatory at age 20 years.

4.7.8 Hypotheses to be tested

This study will test the hypotheses that allocation to one or other treatment arm will be associated with a difference in cognition (HUI); hearing (HUI supplemented by specific audiological studies); emotion (HUI and SDQ); attention, behaviour and peer relationships (SDQ); perceived quality of life (PedsQL, PEDQOL, CHQ-PF28 or QLQ-C30 as applicable); height; sitting height; onset and progress of puberty; hormonal deficiency and glandular toxicity (gonadal and thyroid function tests) in the light of hormone supplementation. Interrelationships between endocrine function, Health Status and QoL will be examined.

5. ELIGIBILITY

5.1 Inclusion criteria

a) Age at diagnosis at least 4 years or 5 years (according to the policy of the National Brain Tumour Group) and less than 22 years.

The date of diagnosis is the date on which surgery is undertaken.

b) Histologically proven medulloblastoma, including the following variants (WHO classification – 2000):

- classic medulloblastoma
- nodular / desmoplastic medulloblastoma
- melanotic medulloblastoma
- medullomyoblastoma

Studies of large cell medulloblastoma indicate that this variant is associated with an aggressive biological behaviour and that it constitutes an independent risk factor for a poor prognosis. Consequently, patients withthe large cell variant of medulloblastoma are ineligible for entry into HIT-SIOP PNET 4. Large cell medulloblastomas are clearly defined in the WHO classification of CNS tumours, making up ~5 % of medulloblastomas. However, central pathology review is required before excluding patients with this variant from the trial (see Appendix D). The PNET 4 National Co-ordinator (Dr B Pizer) or the Chair of the UKCCSG PNET Group (Dr R Taylor) should be contacted for advice with regard to treatment of this tumour sub-type.

Although not required before study entry and randomisation, central pathology review of other variants is considered mandatory (see Appendix D).

c) No CNS metastasis on MRI –
(supratentorial, arachnoid of the posterior fossa or spine)

It is recommended that MRI scan of the head and spine be performed before surgery.

If spinal axis imaging has not been performed before surgery, it should be performed before lumbar puncture in order to avoid artefacts (if positive in such circumstances, spine MRI should be repeated).

Although pre-operative MRI is recommended, a patient is eligible for randomisation/study entry if a CT scan of the head and not MRI is performed pre-operatively - provided an MRI of the head is performed post-operatively to exclude intracranial metastases and this scan is unequivocally negative. Prerandomisation neuroradiological imaging review for the head and spine is strongly suggested but not mandatory. It will be left to national policy.

d) No clinical evidence of extra-CNS metastasis

e) No tumour cells on the cytospin of lumbar CSF. Central Review of CSF cytology is recommended but not mandatory. It will be left to national policy.

Lumbar puncture should generally be performed at least 15 days following surgery, and before randomisation. If a lumbar puncture is performed before 15 days and is negative for tumour cells than this will be taken as evidence of non-metastatic disease. If, however, the CSF is positive by lumbar puncture before 15 days then the lumbar puncture must be repeated at 15 days or beyond to determine M1 status.

Involvement of CSF pathways by tumour is defined as the unequivocal identification of primitive neuroectodermal cells, either on cytological grounds or with a combination of cytological and immunohistochemical features (e.g. reactivity for GFAP or a neuronal marker, such as synaptophysin).

f) Intention to start radiotherapy no more than 40 days after surgery.
(patients will not be removed from study if radiotherapy starts after 40 days post surgery)

g) Ability to receive twice daily radiotherapy.

h) Vital functions within normal range for their age group.

i) CTC grades < 2 for liver, renal, haematological and audiological function.

j) No medical contraindication to radiotherapy or chemotherapy.

k) Written informed consent (and patient assent where appropriate) according to the laws of each participating country. Written informed consent should also be sought for biological studies.

l) National and local ethical committee approval according to the laws of each participating country (to include approval for biological studies).

Patients with residual disease of any size following surgery are eligible for inclusion into the trial (section 4.2.2). The Study Committee do, however, suggest that second look surgery be considered in patients with significant residual disease following primary surgery.

5.2 Exclusion criteria

a) One of the inclusion criteria is lacking

b) Brainstem or supratentorial primitive neuroectodermal tumour.

c) Large cell medulloblastoma

d) Atypical teratoid rhabdoid tumour.

e) Medulloepithelioma.

f) Ependymoblastoma

g) Metastatic medulloblastoma (on CNS MRI and/or positive cytospin of postoperative lumbar CSF)

h) Patient previously treated for a brain tumour or any type of malignant disease.

i) Patients who are pregnant.

j) Females who are sexually active and not taking reliable contraception.

k) Known predisposition to medulloblastoma e.g. Gorlin's syndrome.

6. DIAGNOSTIC STAGING AND INITIAL INVESTIGATIONS

6.1 Preoperative period

a) Clinical examination with full neurological examination.

b) Whole brain imaging - MRI of brain pre and post contrast is strongly recommended in preference to CT scan with contrast.

3D tumour measurements should be undertaken.

c) MRI of the spine with visualisation of the end of the dural sac.

6.2 Post operative period (see appendix G)

a) Cerebral MRI pre and post contrast injection.

<u>Performed within 72 hours after surgery – Ideally between 24 and 48 hours of surgery</u>

Postoperative scanning with MRI of brain, pre- and post-contrast, is strongly recommended in preference to CT scan with contrast, although cerebral CT scan without and with contrast injection is acceptable for local staging. The CT should be performed within 72 hours after surgery.

The size of any post operative residual tumour will be recorded.

b) MRI of the craniospinal axis with visualisation of the end of the dural sac.
(if not performed preoperatively)

c) Lumbar puncture for CSF cytology.

Lumbar puncture should generally be performed at least 15 days following surgery, and before randomisation. If a lumbar puncture is performed before 15 days and is negative for tumour cells than this will be taken as evidence of non-metastatic disease. If, however, the CSF is positive by lumbar puncture before 15 days then the lumbar puncture will be required to be repeated at 15 days or beyond to determine M1 status.

Involvement of CSF pathways by tumour is defined as the unequivocal identification of primitive neuroectodermal cells, either on cytological grounds or with a combination of cytological and immunocytochemical features (e.g. reactivity for GFAP or a neuronal marker, such as synaptophysin).

d) Full neurological examination for neurosurgical evaluation, endocrine status and HUI, SDQ and QoL questionnaires.
To be performed after registration/randomisation and before the start of radiotherapy.

Information concerning premorbid health status and development, birthweight and parental heights, timing of puberty/menarche (where applicable) will be recorded at this time point.

e) Audiology – Pure Tone Audiometry if possible.

f) Full blood count.

g) Blood biochemistry – electrolytes (ionogram), urea, creatinine, ALT, AST, Alkaline phosphatase, bilirubin, albumin, magnesium, calcium, phosphate).

h) Endocrine status: Weight, standing and sitting height, Pubertal staging (Tanner), blood hormone concentrations (see Appendix M).

The PNET 4 treatment (e.g. the use of CCNU and scatter doses of radiotherapy) has the potential to affect subsequent fertility especially in males. Treating clinicians are encouraged to consider and discus this issue with patients/parents and to undertake fertility conservation measures (e.g. sperm storage) in appropriate individuals.

7. STUDY ENTRY and RANDOMISATION

Randomisation will be stratified for each country or group of countries and will be undertaken separately in each national data centre i.e. CRCTU, HIT, Italy, Nordic countries and SFOP. Further stratification will be by the presence or absence of residual tumour after surgery and by sex. Blocked randomisation will be balanced, using tables of random numbers, in order to ensure that there are equal numbers of patients in each treatment group (50% in each arm) at the end of the inclusion period. Block size may vary from one country to another, but will be a function of the number of patients to be included in the trial.

- **Randomisation is Mandatory for Entry into the Study.**
- **Randomisation must be performed within 28 days following surgery.**
- **Registration will only be permitted following confirmation of LREC approval – to be sent to the CRCTU.**
- **Registration and Randomisation into the study will be conducted at the CRCTU by Faxed Registration Form:**

CRCTU Trial Co-ordinator: TBA

Children's Cancer Trials Team
Cancer Research UK Clinical Trials Unit (CRCTU)
School of Cancer Sciences
University of Birmingham
Birmingham B15 2TT

Tel: +44 (0)121-415-8572

Fax: +44 (0)121-414-3700

Office Hours: Monday - Friday 0900-1700

- **The Registration/Randomisation Form will confirm eligibility** (section 5.1) **and exclusion** (section 5.2) **criteria.**

Upon receipt of the Registration/Randomisation Form the CRCTU will return the Form by Fax within 1 working day.

- **The returned form will:**

  1) Confirm suitability for entry into the study

2) Assign a Study Number to the patient

3) Assign the Randomised Radiotherapy to be Administered –

Standard Fractionation Radiotherapy or

Hyperfractionated Radiotherapy

All National Data Centres will send a copy of the Registration/Randomisation Form to the International Data by Fax within 24 hours.

For an eligible patient who is not randomised/entered into PNET 4 due to patient, parent or physician choice, the UKCCSG Brain Tumour Group recommend that the patient receives treatment with the standard arm of PNET 4 i.e. Once daily radiotherapy (23.4 Gy craniospinal dose) with weekly vincristine followed by eight planned courses of CCNU, cisplatin and vincristine chemotherapy. This recommendation applies for carefully staged Standard Risk patients as defined in the PNET 4 protocol.

Trial data will not be collected on patients not randomised/entered into PNET 4.

Consent for Biological Studies

Biological studies are a fundamental part of the PNET 4 Trial. An important secondary aim of this study is to study a number of biological variables in order to determine prognostic factors in medulloblastoma and to enable subsequent stratification of patients according to biological risk groupings.

It is considered mandatory that all patients/families of patients entered into this trial will be approached to consent for collection and banking of tumour specimens. Consent for biological studies will be obtained using the same consent form as that for entry in the study.

It still strongly recommended that consent also be obtained for banking of tumour specimens under the general CCLG scheme for tumour banking - 98 BS 05 (MREC/98/04/023). This is to allow future biological studies not included in the PNET 4 study to be performed.

8. RADIOTHERAPY PHASE

All patients receive radiotherapy (RT) to the craniospinal axis (CSRT). This will be followed by RT to the posterior fossa. In the HFRT arm there will be a final phase of RT directed at the tumour bed.

Before the start of radiotherapy, the treating radiotherapist is strongly recommended to study the radiotherapy data forms to become familiar with the data that is to be recorded, with particular respect to target volumes and critical organs.

8.1 Timing of Radiotherapy (RT)

Following definitive surgery - patients should if possible begin RT within 40 days and preferably within 28 days.

Participating institutions should ensure that patients randomised to HFRT will not require a greater time to start of RT as compared to those patients receiving conventionally fractionated RT.

8.2 Equipment

Modality: Photon RT from a linear accelerator shall be used for the cranial (whole brain) fields and generally for the spinal fields. The use of electron spinal fields will be acceptable provided a beam of sufficient energy is available to ensure adequate irradiation of the target volume allowing for tissue heterogeneity and the junction between the photon cranial fields and spinal electron field can be precisely calculated and implemented.

THE USE OF COBALT IRRADIATION IS UNACCEPTABLE

It is essential that within each treating centre the choice of modality for spinal treatment is standard for each arm of the trial. For example, electron fields must not be used for patients in the conventional arm of the trial if, for logistic reasons, they cannot be used in the hyperfractionated arm.

8.3 Energy

The cranial (whole brain) fields shall be treated with megavoltage photons with energies in the range of 4-6 MV. Energies more than 6 MV should be avoided because of under-dosage to the lateral meninges due to dose built up effect. The posterior fossa and tumour bed RT will usually be given with a higher energy. Photons of energy 4-6 MV will generally be used for spinal irradiation but electrons of suitable energy can be used as an alternative.

8.4 Position for treatment

Patients should be immobilised using an immobilisation system according to local practice. The patient should be maintained in the same position for the cranial and spinal components of CSRT for the duration of this treatment phase.

8.5 Simulator

Planning CT is strongly recommended for definition of the target volume for the craniospinal axis, posterior fossa and tumour bed volumes. It is recommended that the CT slice thickness should be no greater than 0.5 cm in the region of the cribriform fossa, base of skull, posterior fossa and cranio-cervical field junction, and no greater than 1.0 cm elsewhere within the craniospinal axis.
The following target volumes will be outlined:

Craniospinal axis
Posterior fossa
Tumour bed (for the final phase in the HFRT arm)

The following Organs At Risk (OARs) will be outlined:

Eye lenses, optic nerves, pituitary, inner ear, optic chiasm, brain stem, thyroid gland.

For details – see radiotherapy data forms.

Dose Volume Histograms (DVHs), if available should be constructed for the planning target volumes (PTVs) and OARs.

If the spinal field is treated with electron beams the dose along the entire spinal axis should be calculated with an appropriate correction for tissue heterogeneity.

If CT planning is not available then conventional planning of the target volumes is acceptable. Planning CT exam is strongly recommended, particularly for the posterior fossa and tumour bed target volumes.

8.6 Three-dimensional planning

It is strongly recommended that 3-D planning should be used to determine the target volume for posterior fossa and tumour bed. Some centres may wish to consider 3-D planning for determination of CSRT target volume.

8.7 Treatment volume anatomical description and dose

8.7.1 Target Volume

Craniospinal Axis:

The Clinical Target Volume (CTV) for CSRT comprises the whole brain as well as the spinal cord and thecal sac.

Whole Brain Volume
The whole brain CTV should extend anteriorly to include the entire frontal lobe and cribriform plate region. In order to include the cribriform fossa within the CTV, and allowing an additional appropriate margin for PTV, the edge of the field (i.e. the geometric edge of the shielding block) would in many cases include the lenses. Previous studies from SFOP have demonstrated that provided the edge of the shielding block is at least 0.5 cm below the cribriform fossa an increased risk of frontal recurrence has not been observed. Thus the geometric edge of the shield on the film should extend at least 0.5 cm inferiorly below the cribriform plate and at least 1 cm elsewhere below the base of the skull (paying particular attention to the margin around the inferior aspect of the temporal lobes). The margin between the shielding and the anterior border of the upper cervical vertebrae should be 0.5 cm. The lower border of the cranial fields should form a precise match with the upper border of the spinal field.

Cervical Spinal Volume
As much as possible of the cervical spinal volume is included in the lateral cranial fields with the junction between the cranial and spinal fields kept as inferior as possible. This is advised for two reasons:

- Avoidance of as much thyroid tissue irradiation as possible, by shielding this within the cranial volume.

- To minimise the risk of the junction being close to the primary tumour and thus the risk of a 'cold spot' in this region.

The spinal field should extend superiorly to form an accurate match with the border with the lower borders of the cranial fields.

Dorso-Lumbar Spine Volume
The inferior limit of the spinal CTV must be determined by imaging the lower limit of the thecal sac on a spinal MR and will usually extend inferiorly to at least the lower border of the second sacral vertebra.

Width of the Spinal Volume
The aim is to include the entire subarachnoid space including the extensions along the nerve roots as far as the intervertebral foramena. The spinal CTV should extend laterally to cover the intervertebral foramina. An additional margin, generally 1.0 cm on either side should be added for PTV, and an appropriate field width chosen to allow for this. The use of a 'spade' shaped field to treat the lumbo-sacral spine is not recommended.

Posterior Fossa Volume
It is strongly recommended that the CTV for the posterior fossa should be determined on a planning CT. This volume encompasses the entire posterior fossa for the conventional arm (total dose 55.8 Gy) and until 60 Gy in the HFRT arm. The CTV should encompass the following:

- Superiorly - the tentorium

- Inferiorly - the extension of the spinal meninges 2 cm below the lower limit of the tumour as defined on the pre-operative scan. The resulting inferior field edge should at least include the outer table of the skull at the foramen magnum with a safety

margin of 1 cm to assure a reliable coverage of the entire posterior fossa meninges.

- Anteriorly - 1.5 cm anterior to the limit of the tumour on a pre-operative MR.
  This will facilitate the use of posterior oblique fields to reduce the RT dose to the middle ear.

- Posteriorly - the posterior extension of the meninges as far as the inner table of the skull.
  The CTV should include any herniation of the meninges through the craniotomy defect.

- Laterally - the lateral extension of the meninges around the cerebellum

For PTV, an additional margin should be allowed according to departmental policy. This will generally be a margin of 0.5 cm.

A field arrangement using posterior oblique fields is strongly recommended. The purpose of this is to minimise the RT dose to the middle ears.

If CT planning is not available, then the CTV for the posterior fossa should be determined as follows:

The field edge should include a 1 cm margin around the tentorium. The superior field edge will generally extend to 1 cm above the midpoint of a line drawn between the foramen magnum and the vertex. The posterior field edge will generally extend to the outer table of the skull. The field edge should extend anteriorly to the posterior clinoid (the pituitary should be shielded unless tumour had extended to that region) and inferiorly to the outer table of the skull at the foramen magnum with a safety margin of 1 cm to assure a reliable coverage of the entire posterior fossa meninges.
The field arrangement will generally consist of lateral opposed fields.

Beam energy for PF treatment planning
In CT assisted treatment planning the selection of beam energy will depend on the requirements of the ICRU 50/62 rules with respect to dose homogeneity within the PTV. In conventional treatment planning (lateral opposed fields) no energies higher than 6 MV should be used to avoid underdosage in the area of the lateral meninges.

Tumour Bed Boost
This phase applies to the HFRT arm only (the final 8 Gy in 8 fractions). The CTV for this phase should include the original tumour bed only i.e. the postoperative situation. The CTV includes the tissues that previously surrounded the tumour prior to resection, with a 0.5 cm margin. For PTV, an additional margin should be allowed according to departmental policy. This will generally be a margin of 0.5 cm. The field arrangement will be chosen to provide a high conformity index, avoiding OARs where possible.

If CT planning is not available, then the CTV for the tumour bed boost should be determined by conventional planning as follows:

The CTV includes preoperative extent of the tumour with a margin of 1 cm. An additional margin should be allowed for PTV according to departmental policy. This will generally be 0.5 cm. The field arrangement will generally be lateral opposed fields.

Imaging for treatment planning (PF boost)
It is recommended the following imaging techniques be used for computer assisted treatment planning:
The definition of tumour spread at diagnosis (preoperative) should be based either on CT with contrast or MR T1 weighted with contrast. For postoperative definition of CTV for treatment planning, a CT with or without contrast should be used for the scans on which the CTV is delineated. Postoperative MR - T1 weighted images with contrast or CT with contrast (away from the treatment planning position) should be performed to identify and delineate possible residual disease that has to be included into the CTV. Use image fusion whenever possible!
If CT planning is not available, MR with contrast or CT with contrast preoperatively should be used for treatment planning.

8.7.2 Dose Specification

Dose Definition: All doses will be specified according to ICRU 50/ICRU 62.

8.7.3 Reference Point

Brain
If the brain is treated by a pair of parallel opposed fields, the dose should be defined at the midpoint of the central axis.

Spine
The dose to the spine should be prescribed along the central axis at a depth representing the posterior margin of the vertebral bodies.
In the case of electron RT to the spine the anterior border of the target volume (posterior aspect of the vertebral bodies) must be encompassed within the 85% isodose.

Posterior Fossa
The prescription point should be in the centre of the target volume, i.e. at the intersection point of oblique fields or along the central axis of the opposed beams, midway between the two entrance points. Note that the dose contribution to the posterior fossa dose from the whole brain fields should be considered equal to the dose prescribed to the whole brain. Correction for decreased separation should not be made.

8.7.4 Total Treatment Dose

Standard RT Regimen

Brain – 23.40 Gy in 13 daily fractions of 1.80 Gy
Spine - 23.40 Gy in 13 daily fractions of 1.80 Gy
Primary tumour boost – 30.6 Gy in 17 daily fractions of 1.80 Gy
Total dose to primary – 54 Gy in 30 daily fractions of 1.80 Gy

HFRT Regimen

Brain – 36.00 Gy in 36 twice-daily fractions of 1.00 Gy
Spine - 36.00 Gy in 36 twice-daily fractions of 1.00 Gy
Posterior fossa – 24.00 Gy in 24 twice-daily fractions of 1.00 Gy
Tumour bed boost – 8.00 Gy in 8 twice-daily fractions of 1.00 Gy
Total Dose to Primary – 68 Gy in 68 twice-daily fractions of 1.00 Gy

Time Dose Considerations:

Standard RT Regimen: Daily fractions.
Mondays – Fridays, 5 days per week.

HFRT Regimen: Twice Daily Fractions will be used.
Mondays – Fridays, 5 days per week.

The minimum time interval between fractions will be 8 hours

The dose per fraction will be 1.80 Gy in the conventional RT arm and 1.00 Gy in the HFRT arm.

Standard Fractionation Regimen
1.8 Gy daily, 5 fractions per week
Cranio-spinal axis:
23.4 Gy in 13 fractions of 1.8 Gy
Posterior fossa:
30.6 Gy in 17 fractions of 1.8 Gy

Hyperfractionated RT (HFRT)
1 Gy b.d. (minimum interval between fractions 8 hours). 10 fractions per week
Craniospinal axis:
36 Gy in 36 fractions of 1 Gy
Posterior fossa:
24 Gy in 24 fractions of 1 Gy
Tumour Bed:
8 Gy in 8 fractions of 1 Gy

Fractionation
All fields should be treated daily (conventional RT) or twice daily (HFRT), 5 days per week.

Rests
There will be no planned rests. Delays due to machine services and bank holidays should be avoided wherever possible.

Modifications due to Haematological Toxicity

Thrombocytopaenia
Radiotherapy will continue uninterrupted unless a platelet count of < 25 x 10^9/L is observed. If a platelet count of < 25 x 10^9/L occurs, then the craniospinal component of radiotherapy is interrupted but the Posterior Fossa boost will continue to be given. CSRT will restart when the platelet count has recovered to > 50 x 10^9/L unsupported by platelet transfusions. In addition, if the patient develops a platelet count of < 25 x 10^9/L, then transfusions of platelets should be given to maintain the count above this level in order to prevent CNS haemorrhage.

Neutropaenia
If a neutrophil count of < 0.5 x 10^9/L occurs, then the craniospinal component of radiotherapy is interrupted but the Posterior Fossa boost will continue to be given.
If a neutrophil count of < 0.5 x 10^9/L occurs, then G-CSF 5ug/kg (s/c or i/v) may be given daily to maintain a neutrophil count of > 0.5 x 10^9/L. If given, G-CSF should continue until the neutrophil count rises to > 1.0 x 10^9/L for two successive days. CSRT will restart when the neutrophil count has recovered to > 1.0 x 10^9/L whether or not the patient is receiving G-CSF.

Anaemia
The haemoglobin level should be maintained at a minimum level of 10 g/dL during RT by transfusion if necessary.

8.7.5 Dose Uniformity and Reference Points

Brain, Posterior Fossa and Tumour Bed
Homogeneity of +7%, -5% relative to the prescription point is required (ICRU 50).

Spine
The maximum dose variation along the longitudinal axis of the spinal cord should be +7% to
-5%. Tissue compensations may be required to achieve this degree of dose uniformity. The dose to the cord at the level of C5 and L3 should be recorded.

8.7.6 Treatment Technique

Cranial RT
The cranial fields will be treated with lateral opposed fields.

Spine Irradiation
If possible the spinal volume should be treated with a single posterior field. If necessary the spinal field can be treated at an extended FSD. The exit from the spinal field should not include the teeth.

Junctions
Junctions of abutting fields should be moved either on a daily rotating basis or weekly (moving junction technique).

Posterior Fossa
It is strongly recommended that the posterior fossa should be treated by posterior oblique fields angled to reduce the RT dose to the middle and inner ear. This is considered ideal in an attempt to minimise the risk of ototoxicity resulting from an interaction between RT and cisplatin. Customised divergent beam blocks or multileaf collimators should be used.

Primary Tumour (HFRT Arm)
It is strongly recommended that this volume should be treated conformally. The field arrangement will be chosen to provide a high conformity index and to minimise the RT dose to OARs. If conformal planning is not available than it is acceptable to treat this volume with lateral parallel opposed fields.

Intensity Modulated Radiotherapy (IMRT)
It is likely that during the duration of this study, IMRT planning and delivery techniques will be increasingly employed. As an example, this may be used as an option for reducing the radiation dose to the cochlea. IMRT has also been used to improve homogeneity of spinal RT. If centres employ IMRT then it will be essential to observe strict criteria for immobilisation and departmental quality assurance. In addition, it will be essential that centres employing IMRT should do so for patients treated in both arms of the study.

8.8 Quality control of radiotherapy

Radiotherapy for patients with the diagnosis of a medulloblastoma requires a complex treatment technique. It has been previously clearly demonstrated that the relapse risk is closely related to the quality of radiotherapy.

Thus in PNET 4 quality control (QC) of the radiation technique is considered a fundamental component of the study, particularly in the context of reduced dose craniospinal radiotherapy (23.4 Gy), where sub optimal radiotherapy may have a greater significance than protocol deviations where 35 – 36 Gy craniospinal radiotherapy is given. Although not mandatory, most National Groups will attempt to undertake radiotherapy QC as early as possible to enable corrections for major deviations from the protocol. In these groups, QC will be performed either prior to the start of radiotherapy or at the latest within one week of the first fraction.

General Organisation of Radiotherapy QC

- Radiotherapy QC will be organised and undertaken on a National basis. This should include a procedure to reproduce and check target volumes and dose prescription.

- Each National Group will appoint a National Radiotherapy Coordinator

- The National Radiotherapy QC Coordinator will work in close co-operation with two to three named radiotherapy colleagues forming the National Radiotherapy QC panel. This will ensure the constant availability of a QC assessor without delay. Submitted films will be assessed and returned (if originals were submitted) within 72 hours following receipt. Otherwise the submitting center will be informed via fax or e-mail of the QC assessment result.

- Submission of planning documentation - imaging or computer generated dose distributions (i.e. either electronically or via courier) may vary from country to country. Each national group will decide on the most appropriate way of submitting films and plans. Guidance can be obtained from the National Radiotherapy Coordinator.

- Radiotherapy QC committees will meet three times a year. They will review the current status of compliance with the aim of prospective QC control and review films or scans submitted during the last 4 months. They will provide an annual report that will include any targeting deviations. This report will be sent to the National Study Coordinator, the International Radiotherapy Coordinator and the International Data Centre.

- Countries who do not wish to set up their own QC panel should at the start of the study identify the QC panel of a National Group of their choice, which will provide the prospective QC for them.

QC of Craniospinal Radiotherapy

- <u>In PNET 4 quality control of the craniospinal part of the treatment is mandatory</u>.

- Some National Groups or centres within National Groups will investigate the feasibility of Radiotherapy QC including verification of planning films before the start of radiotherapy in order to correct any possible protocol deviation in relation to in the definition of irradiation fields.

- For most centres, copies of craniospinal RT planning films and treatment charts should be sent to the National Radiotherapy QC panel within one week of the start of RT again to correct any possible flaw in the definition of irradiation fields.

- For <u>all patients</u>, radiotherapy QC will be undertaken within one year of diagnosis.

Copies of the following imaging for treatment planning (e.g. simulator films, digitally reconstructed radiographs –DRR's-) should be sent to the National Radiotherapy QC panel (preferably by electronic transfer of digitised images):

1. Whole brain field
2. Spinal field/fields

Any targeting deviations will be defined as either minor or major.

The deviation is defined as a margin between the field edge and the CTV of less than 5 mm for the cribriform fossa and less than 10 mm for field edges elsewhere within the whole brain.
For the cribriform fossa a minor deviation is defined as a margin of 3-5 mm and a major deviation a margin of less than 3 mm.

For the other regions a minor deviation is defined as a margin of 5-10 mm and a major deviation a margin of less than 5 mm. For details see radiotherapy data forms.

QC review of posterior fossa and tumour bed

QC review of posterior fossa and tumour bed target volumes will be organised on a national level.

- Radiotherapy QC of the posterior fossa component is not mandatory unless the patient experiences a posterior fossa relapse (see below) in which case a retrospective QC review is mandatory.

- Some National groups may, however, wish to conduct prospective QC of posterior fossa radiotherapy. If such prospective QC is undertaken, then the National Radiotherapy QC panel will be responsible for determining the criteria by which posterior fossa treatment techniques are evaluated.

- For some National Groups Radiotherapy QC of the posterior fossa component will be organised on the basis of national educational 'workshops'.

- All patients who relapse within the posterior fossa either alone or in combination with other sites will undergo a separate radiotherapy QC. Centers will be requested to provide the documentation of their posterior fossa and/or tumor bed boost together with the diagnostic imaging at diagnosis and relapse. The radiotherapy QC panel, in collaboration with appropriate neuro-radiologists if indicated, will determine the exact site of relapse as a function of irradiation volume.

UK Radiotherapy Quality Control:

Radiotherapy QC for the UK will follow the guidelines as laid out in section 8.8 of the PNET 4 protocol.

The craniospinal axis treatment will be prospectively evaluated either before the first fraction or within 5 working days from the start of radiotherapy. Either original or copies of simulator films (for conventionally planned patients) or DRRs will be sent either by post or electronically to the national co-ordinator or a named QC reviewer and will be returned within 72 hours.

If simulator films are submitted for review, the package should include:

- simulator films (original or copies) of the whole CNS field including either the marked outline for the blocks or preferentially block verification films if done.
- simulator verification film (original or copies) for the spinal axis field including a documentation of any shielding used.

All original films will be scanned for future reference and immediately returned.

If the patient is primarily CT planned, the following documentation should be submitted:

- colour printout of the axial and sagittal dose distribution at the isocenter of the whole CNS field.
- colour printout of the craniospinal axis dose distribution in a sagittal view.
- printout of the DVH for the whole planning target volume.
- simulator (preferentially) or verification film demonstrating the final whole CNS field with the shielding used.

The simulator film is required as it is anticipated that the an assessment of the chosen leading for the CNS as outlined in the QC requirements (e.g. cribriform plate) is unlikely to be feasible and sufficiently accurate on printouts. The printouts will remain with the QC panel and the submitted simulator film will be scanned and returned immediately.

Following the assessment, the result of the QC process will be faxed or e-mailed to the submitting clinician and the original film(s) returned per post. If a major deviation is noted on the QC assessment, the treating clinician should correct the treatment of the patient but no further central review will be required.

Once the CRCTU Data Centre is notified of a patient suffering a relapse including any part of the posterior fossa, the treating clinician will receive a request to provide within 6 weeks:

- the whole radiotherapy documentation including the posterior fossa and/or tumour bed boost.
- the diagnostic imaging at diagnosis, immediate postoperative and relapse (original or representative copies).

At the next meeting the radiotherapy QC panel, in collaboration with appropriate neuro-radiologists if indicated, will determine and document the exact site of relapse as a function of irradiation volume and return submitted original films.

To submit planning films for the quality control process, contact the QC co-ordinator either via fax, telephone or e-mail prior to sending any scans. The co-ordinator will confirm on the same working day if he is able to perform the QC. If he is unable to review the films within the set time frame he will recommend an alternative reviewer to whom the information should be sent.

The QC panel will meet three times per year to review jointly submitted films and report on an annual basis to the National Trial Co-ordinator.

The following three clinical oncologists constitute the national QC panel:

Frank Saran (co-ordinator)
Department of Radiotherapy
Royal Marsden Hospital NHS Trust
Downs Road
Sutton,
Surrey, SM2 5PT
Tel: 0208-661 3826 (sec)
0208-642 6011 (switchboard)
Fax: 0208-661 3470
E-mail: frank.saran@rmh.nthames.nhs.uk

Roger Taylor
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Tel: 0113-392 4399
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Michael Williams
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E-mail: michael.williams@addenbrookes.nhs.uk

ON LINE RADIOTHERAPY QUALITY CONTROL

DIAGNOSIS OF MEDULLOBLASTOMA

↓

☎

CALL TO RADIATION ONCOLOGIST
IN ORDER TO PREPARE RADIOTHERAPY

This should be done prior to study entry to prevent any delay in starting radiotherapy.

↓

IMMOBILIZATION DEVICE + CT PLANNING/SIMULATION

↓

SEND WHOLE BRAIN AND SPINAL FIELD
SIMULATOR FILMS
(e-mail💻, fax or rapid courier ✉)
TO NATIONAL RADIOTHERAPY QC PANEL

↕

FEEDBACK FROM RADIOTHERAPY QC PANEL
– WITHIN 72 HOURS

START OF RADIOTHERAPY
IF POSSIBLE WITHIN 40 DAYS
OF SURGERY
(PREFERABLY WITHIN 28 DAYS)

Note: The Schema for Radiotherapy QC is independent of randomisation i.e. it is the same for Standard RT and HFRT

8.9 Chemotherapy during the radiotherapy phase

- All patients receive chemotherapy during irradiation.
- A total of 8 doses of vincristine will be administered.
- The first will be given during the first week of RT.
- Treatment with weekly vincristine will thus usually extend beyond the end of radiotherapy.
- Weekly administration of vincristine will be suspended for breaks in radiotherapy due to myelosuppression or other reason and will recommence when radiotherapy is restarted. In this case, eight doses of vincristine will still be given unless toxicity due to vincristine necessitates omission of this drug.

Vincristine 1.5 mg/m^2 (maximum dose 2 mg).

Dose modification of vincristine:

Epileptic seizure **Ileus**	**or**	Stop VCR in this course and reduce VCR to 1 mg/m^2 in the next course
	After recovery	Give VCR at 100% doses
Significant dysaesthesia, muscular weakness or abdominal pain		Omit VCR until recovery
	After recovery	Give VCR at 100% doses

8.10 Assessment during and following radiotherapy

Weekly:

- Clinical exam including neurological evaluation
- Full blood count (before each VCR injection)
- Serum biochemistry if clinically indicated (e.g. vomiting, corticosteroid treatment etc)

8.11 Supportive care during and following radiotherapy.

Steroids should not be used routinely during RT. If symptoms of raised intra-cranial pressure develop during treatment the cause, e.g. hydrocephalus, should be actively sought. Dexamethasone may be used as a short-term measure for the treatment of symptoms of raised intracranial pressure or the treatment of nausea and vomiting which cannot be controlled by antiemetics such as 5HT3 antagonists. The lowest dose of dexamethasone consistent with control of symptoms should be used and steroid treatment should be carefully withdrawn as soon as possible.

9. INVESTIGATIONS BEFORE THE CHEMOTHERAPY PHASE

These should be performed just before 6 weeks after the end of radiotherapy:

a) Clinical exam with neurological exam.

b) Cranial MRI with and without contrast injection.

c) MRI of spine to include visualisation of the end of the dural sac.

d) Audiology – Pure Tone Audiometry if possible.

e) Full blood count.

f) Blood biochemistry – electrolytes (ionogram), urea, creatinine, ALT, AST, Alkaline phosphatase, bilirubin, albumin, magnesium, calcium, phosphate).

g) Glomerular filtration rate - by clearance of radioisotope or creatinine clearance (either measured or calculated – see appendix K).

10. MAINTENANCE CHEMOTHERAPY

10.1 Summary of the regimen

Maintenance-chemotherapy starts 6 weeks after the end of radiotherapy.

Each course consists of:

- **Cisplatin** **70 mg/m^2 intravenously (6 hour infusion) - day 1**
- **CCNU (Lomustine)** **75 mg/ m^2 orally - day 1**
- **Vincristine** **1.5 mg/m^2 intravenously (bolus; max. dose 2 mg) - day 1, 8 and 15**

See section 10.3 and Appendices H and J for details of administration

Each course should be planned to be given at 42 day intervals i.e. 6 week cycles.

A total of eight courses are planned.

10.2 Investigations during chemotherapy

10.2.1 Investigations before each course of chemotherapy.

a) Clinical exam with neurological exam.

b) Full blood count.

c) Blood biochemistry – electrolytes (ionogram), urea, creatinine, ALT, AST, Alkaline phosphatase, bilirubin, albumin, magnesium, calcium, phosphate).

d) Audiology (mandatory) – Pure Tone Audiometry if possible.

e) Glomerular filtration rate if estimated from plasma creatinine level (see appendix K).

10.2.2 Investigations before alternate courses of chemotherapy.

All of the above plus:

Glomerular filtration rate (GFR) if estimated by clearance of radioisotope
- in those centres that routinely use this method for measurement of GFR.

10.2.3 Investigations after FOUR courses of chemotherapy.

a) Cranial MRI with and without contrast injection.

b) Spinal MRI to include visualisation of the end of the dural sac.

10.2.4 Investigations after final course of chemotherapy.

a) MRI of the head with and without contrast injection.

b) MRI of spine to include visualisation of the end of the dural sac.

10.3 Chemotherapy administration.

Administration of cisplatin.

In the context of a multicentre international trial, it is appreciated that different national groups and individual centres have varying but well established methods of giving cisplatin.

Precise guidelines for cisplatin administration relevant to each national group are presented in Appendix H.

The following considerations are, however, considered mandatory for the PNET 4 trial:

- **Cisplatin to be given as an infusion over 6 hours**
- **Hyperhydration to be used to maintain an adequate urine output**
- **The use of Mannitol to enhance urine output**
- **The addition of calcium, magnesium and potassium to hydration fluids**
- **The use of 5HT3 antagonists for antiemesis**
- **Careful monitoring of urine output with appropriate guidelines for treatment of insufficient urine output**

Administration of carboplatin (if indicated)

Carboplatin 400 mg/m^2 is to be given as a 1 hour infusion.

The choice of fluid for administration and any pre- or post-chemotherapy fluids will be at centre/group discretion.

10.4 Chemotherapy dose modification.

These guidelines do not replace individual responsibility for patient care!

For advice - please contact study chairman.

Before each course of chemotherapy the patient should be in a good general clinical condition.

10.4.1 Haematological

Full blood count (FBC) should be performed at least every 2 weeks after the start of each course of chemotherapy.

Before each course:

WBC	**< 2 x 10^9/L or**	Delay chemotherapy for at least one week.
Neutrophils	**< 0.5 x 10^9/L or**	
Platelets	**< 100 x 10^9/L**	
Platelet/WBC recovery delays therapy > 2 weeks		Omit CCNU for next course and Reduce CCNU to 50 mg/m^2 in all subsequent courses.
If further episode		Omit CCNU for next and all subsequent courses (give full dose cisplatin).

Nadir after course:

WBC	**< 0.5 x 10^9/L or**	Reduce CCNU to 50 mg/m^2 in the next and all subsequent courses.
Neutrophils	**< 0.05 x 10^9/L**	

and after episode of neutropaenic fever

If further episode (with or without G-CSF administration)		Reduce cisplatin to 50 mg/m^2 in the next and all subsequent ` courses.
Platelets	**< 30 x 10^9/L**	Reduce CCNU to 50 mg/m^2 in the next and all subsequent courses.
	If further episode	Omit CCNU for next and all subsequent courses (give full dose cisplatin).

10.4.2 Neurotoxicity of vincristine

Epileptic seizure Ileus	**or**	Stop VCR in this course and reduce VCR to 1 mg/m^2 in the next course
	After recovery	Give VCR at 100% doses
Significant dysaesthesia, muscular weakness or abdominal pain		Omit VCR until recovery
	After recovery	Give VCR at 100% doses

10.4.3 Nephrotoxicity

- **Nephrotoxicity is a major toxicity of cisplatin. Both glomerular and tubular toxicity must be monitored during treatment with cisplatin.**

- **Dose modification is based on glomerular toxicity i.e. a reduction in Glomerular Filtration Rate (GFR).**

- **In the context of a multicentre international trial, it is appreciated that different national groups and individual centres have varying but well-established methods of measuring or estimating GFR. These include methods based on blood clearance of radioisotope e.g. MAG3 and clearance of ^{51}Cr EDTA or Tc99m DTPA, estimation of creatinine clearance from the plasma creatinine level (e.g. using the Schwartz formula – Appendix K) or by direct measurement of urinary creatinine clearance.**

- **Any well established method of estimating GFR as detailed above may be used prior to chemotherapy.**

- **The estimation of GFR must be performed before the first course and at least before every other course (i.e. before courses 1, 3, 5, and 7).**

Serum creatinine > 1.2 mg/dL (100μM)	**or**	
higher than 1.5 x normal upper limit	**or**	Delay chemotherapy for 1 week
GFR/Creatinine clearance < 80 ml/min per 1.73 m^2		
If no recovery		Perform estimation of GFR by clearance of radioisotope
Isotope GFR ≥ 60 and < 80 ml/min per 1.73 m^2		Use carboplatin 400 mg/m^2 instead of cisplatin for next course. Perform estimation of GFR by clearance of radioisotope before next course
Isotope GFR < 60 ml/min per 1.73m^2		Omit any platinum for next course. Perform estimation of GFR by clearance of radioisotope before next course

10.4.4 Ototoxicity:

The Ototoxicity Grading System in PNET 4 is that used in the HIT 91 and HIT 2000 studies, as follows:

Grade 0: **normal**

Grade 1: **≤ 15 dB at ≤ 2000 Hz**

Grade 2: **16-30 dB at ≤2000 Hz**

Grade 3: **31-60 dB at ≤ 2000 Hz**

Grade 4: **>60 dB at ≤ 2000 Hz**

It is, however, mandatory, for patients to have a Pure Tone Audiogram performed at the end of treatment. This audiogram will be either sent to the National Data centre or the grading recorded on the data forms and be graded according to both the HIT and Brock/CTC grading systems (Appendix L) to enable a comparion of ototoxicity between different treatment studies.

The Dose Modification of cisplatin is based on the sytem used in the HIT 91 and HIT 2000 studies, as follows:

Hearing – PTA	Dose Modification
< 16 dB at 1000-3000 Hz or ≤ 40 dB at 4000-8000 Hz	**None**
16-30 dB at 1000-3000 Hz or > 40 dB at 4000-8000 Hz	**Substitute Carboplatin 400 mg/m^2 for Cisplatin**
> 30 dB at 1000-3000 Hz	**Omit any platinum**

Grading for Audiometry is based on loss in both ears –
Thus the grading (including that for modification of chemotherapy) is based on the Highest Grading i.e. the 'worst ear'.

10.4.5 <u>Body weight</u> (consider supplemental feeding if nutrition compromised)

Loss of body weight greater than 20 % compared to body weight at the end of radiotherapy (or earlier if long term corticosteroids have been needed)	Reduce CCNU in next course to 50 mg/m^2
If further loss of body weight	Omit CCNU for next and all subsequent courses

10.5. Supportive Care during chemotherapy.

- **Anti-emesis:** A 5HT3 antagonist must be used as an anti-emetic for cisplatin-containing chemotherapy.
  <u>Dexamethasone should not be used as an anti-emetic unless other therapies fail</u>.

- **Steroids:** Patients should not be receiving steroid therapy (e.g. dexamethasone) during chemotherapy if at all possible. If symptoms of raised intra-cranial pressure develop during treatment the cause e.g. hydrocephalus should be actively sought. Steroids should be used as a short-term measure prior to definitive treatment of the raised pressure.

11. FOLLOW-UP AFTER TREATMENT

11.1 Oncological Follow-up

- Clinical follow-up – at centre discretion.

- Neuroradiological follow-up:

  For purposes of this study, MRI of head and spine should be performed at least every 6 months for 3 years post treatment. Other imaging is to be performed at the treating physician's discretion.

11.2 Late effects: see Appendix M and table in section 1.5.

11.3 Relapse or Death

- **Tumour relapse or patient death must be notified to the National Data Centre using the appropriate Data Form within one month of the event.**

- **In the case of sudden death due to a SAE – this must be reported within 24 hours of knowledge of the event as with other SAEs (see section 12).**

- **In the event of a relapse that involves the Posterior Fossa, then the appropriate National Radiotherapy QA Group must be informed.**

- **Spinal MR should be performed in the event of a Posterior Fossa relapse to define fully the pattern of relapse and to plan further therapy.**

- **Guidance for the treatment of relapse can be obtained from the appropriate PNET 4 National Co-ordinator.**

12. SERIOUS ADVERSE EVENTS AND TOXICITY REPORTING.

Common Toxicity criteria definitions will be used for toxicity reporting.

The CTC (Appendix L) used in completion of the data forms will be the same for all participating groups.

Definition of serious adverse events (SAEs) is based upon the ICH GCP Guidelines

In this study, a serious SAE is defined as:

Any unexpected medical occurrence that:

- Results in death (death from tumour progression is not an SAE)
- Is life-threatening
- Requires unexpected inpatient hospitalisation or prolongation of existing hospitalisation
- Results in persistent or significant disability/incapacity
- Overdose that leads to symptomatic disease

In addition, for this study the following toxicities will also be defined as SAEs:

- Any grade 3 or grade 4 central neurotoxicity

- Any grade 3 or grade 4 unexpected toxicity

Ototoxicity as a result of cisplatin chemotherapy and radiotherapy to the cochlea is an expected complication of the treatment described in this protocol. As such, ototoxicity, including Grade 3 or 4 ototoxicity, is not regarded as a SAE in this study. The occurrence of ototoxicity will however be carefully monitored and stopping rules are in place for excessive ototoxicity (section 13.7).

Serious adverse events must be reported within 24 hours of the knowledge of the event by fax to the National Centre which will notify both the National Study Co-ordinator and the International Data Centre.

The International Data Centre will be responsible for informing the independent Data Monitoring and Safety Committee and other regulatory bodies as appropriate.

In addition, each National Data Centre will be responsible for informing their appropriate national regulatory bodies as appropriate.

13. STATISTICAL CONSIDERATIONS

13.1 Study design

The study is a comparison between treatment with hyperfractionated radiotherapy and conventional RT with a reduced craniospinal dose in patients with Medulloblastoma without metastases in the age group 4- 21 years. The lowest age limit may differ between national groups but must not be lower than 4 years at the day of surgery. Recruitment of patients will last until 31.12.2005. Thereafter a prolongation of the study is possible, (see 13.5), and will be the case in order to recruit the necessary number of patients to reach the desired statistical power. The information of the about the recruitment rate in the HIT study in the first two years of the trial should not be used. A 2-year observation time will be undertaken following closure of the study.

After parental/patient consent every patient in the study will be randomised to one of the two treatment arms. The randomisation will be by block randomisation undertaken at the relevant National Data Centre. Randomisation will be stratified according to sex and the presence of residual tumour (see 5.1.c) on postoperative scan.

GCP of ICH and the Declaration of Helsinki will be respected in the study.

13.2 Primary Question

Will hyperfractionated RT lead to a different event free survival (EFS) compared to the standard arm RT?

13.3 Secondary Questions

All Patients

1) Will hyperfractionated RT lead to a different progression free (PFS) and overall survival (OS) compared to the standard arm RT?

2) Will hyperfractionated RT lead to a different pattern of local tumour control/pattern of relapse with particular respect to local relapse (tumour bed, posterior fossa outside the tumour bed) compared to the standard arm RT? The time to local progression should be the measure for the local tumour control.

3) Is there a difference in health status, quality of life index, audiological toxicity and endocrinological late effects in patients treated with hyperfractionated RT compared to patients treated with standard RT?

4) The prognostic relevance of biological tumour markers will be studied.

5) The toxicity of neurosurgery will be estimated.

HIT Group Patients: Additional Secondary Questions

1) Will there be a difference in EFS, PFS and OS in patients with hyperfractionated RT compared to historical similar groups in the HIT-91 study with conventional RT without reduction in the craniospinal dose?

2) Is the EFS, PFS and OS in patients with standard RT not worse than the progression free survival in historical similar groups in the HIT-91 study with conventional RT?

3) Is there a difference in intelligence quotient in patients treated with hyperfractionated RT compared to patients treated with standard RT?

4) Will hyperfractionated RT lead to a difference in degree of leucoencephalopathy compared to conventional RT?

5) The following factors should be tested for their prognostic relevance for EFS, PFS and OS:

Histopathological factors
Tumour: preoperative size (biggest diameter in cm)
postoperative size (extent of resection)
localisation/ spread
Secondary effects: Hydrocephalus
Occurrence of metastases
Response to RT
Therapy: Quality/Realisation
Age (continuous : age group in years [4-16], [16-21])
Sex
Size of treatment centre i.e. > 4 patients vs $\leq$ 4 patients yearly

13.4 Definitions

i) Event: The appearance of a relapse (local, metastasis or combined) following previously documented CR, progression (definition below), death for any reason or the appearance of a secondary tumour.

ii) Progression: If previous residual tumour, growth > 25 % (sagittal and coronal diameters in axial slice) on neuroradiological investigation or the appearance of new tumour manifestations.

iii) Event free survival: This time period begins with the day of surgery and ends with the appearance of an event.
Patients lost to follow-up without an event will be censored at the date of their last follow-up.

iv) Progression free survival: This time period begins with the day of surgery and ends with the appearance of a relapse (by previous CR) or progression.
If death occurs that has no relation to the tumour disease or if a secondary tumour appears the patient will be censored to the time point when this event occurs.

v) Time to local tumour progression: For the definition of progression see ii. The appearance of metastases only will not be regarded as local progression**.**

vi) Quality of life: see Appendix M

vii) Audiological toxicity: see section 10.4.4.

HIT Group patients:

i) Intelligence Quotient: see definition in HIT 2000 study protocol – Appendix 5.

ii) Degree of leucoencephalopathy: see definition in HIT 2000 study protocol – Appendix 5.

13.5 Interim and final analyses

Interim analyses will be performed two and four years after the start of the study. The final evaluation with study report will be performed after seven years. If an interim analysis shows significantly superior EFS in one of the treatment arms the study will be closed. If other studies show that the main question of the study is answered, the study steering committee together with the DMSC will decide on closure of the study.

The design of this trial may be changed, if necessary, in case of new important discoveries. Modifications of the protocol will be made only in the form of written amendments and with the agreement of the study committee. The respective ethic commissions have to be informed of the modifications.

If an adjustment of the group sequential design is necessary e.g. because of a low recruitment rate - the respective changes of the time points, number of interim analyses, maximal sample size and a-spending function will be done according to the conditional rejection error probability method by Schäfer and Müller (reference below). The modifications can be done during a planned or unplanned interim analysis on the basis of the observed data collected so far. The corresponding conditional rejection error probability functions are defined by Schäfer (reference below). If a design change is made, the time point, the data file of the trial, all calculations and the description of the new group sequential

design have to be recorded in the amendment.

Reference: Schäfer H, Müller H-H: Modification of the sample size and the schedule of interim analyses in survival trials based on data inspections. *Statistics in Medicine* 2001; 20: 3741-51.

13.6 Serious Adverse Events

Serious Adverse Events (section 12) should be reported to the National Data Centre within 24 hours of the knowledge of the event, which will transmit the information to the International Data Centre. Transmission of this information will be done to the DMSC when appropriate. Toxicity analysis will be performed every 6 months and will be forwarded to the DMSC who will decide whether and how the study will proceed.

13.7 Stopping Rules for Audiological toxicity

A Kaplan-Meier estimation of ototoxicity (p) will be calculated separately for each arm. Any grade 3 or grade 4 toxicity as defined by the HIT Group criteria (section 10.4.4) will be considered as an event. The stopping rule will focus on the Kaplan-Meier estimation for ototoxicity noted on the post treatment audiograms. At these time points the number of toxic events should not exceed 20%.

13.8 Statistical analysis

The analysis follows the Intention to Treat principle. The main question for the whole cohort of patients and for the HIT group will be analysed in hierarchical order with the analysis of the total group of patients at the top of hierarchy i.e. the significant difference of EFS between both arms of RT for HIT patients can only be achieved if a significant difference of EFS has already been shown for the total group of patients. For the two interim analyses of the main question a significance level of 0.005 will be used in each case. For the final analysis of the main question a significance level of 0.04 will be used. The overall significance level will be equal to 0.05.

The p-value of the tests to answer the secondary questions below will be regarded as explorative.

Corresponding to the main question, the following null-hypothesis and statistical tests will be used:

1. Null hypotheses: The EFS between patients with HFRT and standard RT is not different for the whole group nor for the HIT patients. These hypotheses will be tested with a two-sided log-rank test. Patients will contribute with all their follow up time to the analysis. To illustrate the course of events, hazard and survival function (including the 2, 3 and 5-year survival) in both therapy arms will be estimated.

Corresponding to the secondary questions, the following null-hypotheses and statistical tests will be used:

2. Null hypotheses: The PFS and OS in patients with HFRT and standard RT is not different. These hypotheses will be tested with a two sided log-rank test. Patients will contribute with all their follow up time to the analysis. To illustrate the course of events hazard and survival function (including the 2, 3 and 5-year survival) in both therapy arms will be estimated.

3. Null hypothesis: The time to local tumour progression in patients with HFRT and standard RT is not different. This hypothesis will be tested with a two sided log-rank test. Patients will contribute with all their follow up time to the analysis. To illustrate the course of events hazard and survival function (including the 2,3 and 5-year survival) in both therapy arms will be estimated.

4. Null hypotheses: There is no difference in health status, behaviour, audiological toxicity and endocrinological late effects or quality of life in patients with HFRT compared to patients with standard RT.

HIT Group patients:
1. Null hypothesis: The EFS, PFS and OS between patients with HFRT is not different from the EFS, PFS and OS in the historical similar group in the HIT-91 study with standard RT without reduction of the craniospinal dose. These hypotheses should be tested with a two sided log-rank test.

2. Null hypothesis: The 4 year EFS-, PFS- and OS-survival rate in patients with standard RT is smaller than the 10% reduced 4 year EFS-, PFS- and OS-survival rate in the historical similar group in the HIT-91 study with standard RT. These hypotheses should be tested with a one sided log-rank-test.

3. Null hypothesis: There is no difference in the intelligence quotient in patients with HFRT compared to patients with standard RT. This hypothesis should be tested with a two sided Wilcoxon test for unrelated samples.

4. Null hypothesis: There is no difference in the grade of leucoencephalopathy in patients with HFRT compared to patients with standard RT. This hypothesis should be tested with a two sided Wilcoxon test for unrelated samples.

5. The importance of the prognostic factors for No. 5 of the secondary questions for HIT Group patients listed in section 13.3 on EFS, PFS and OS will be estimated with Cox-regression analysis.

13.9 Per protocol analysis

A per protocol analysis will also be carried out to study stability of results, but confirmatory conclusions will depend on the Intention to Treat analysis.

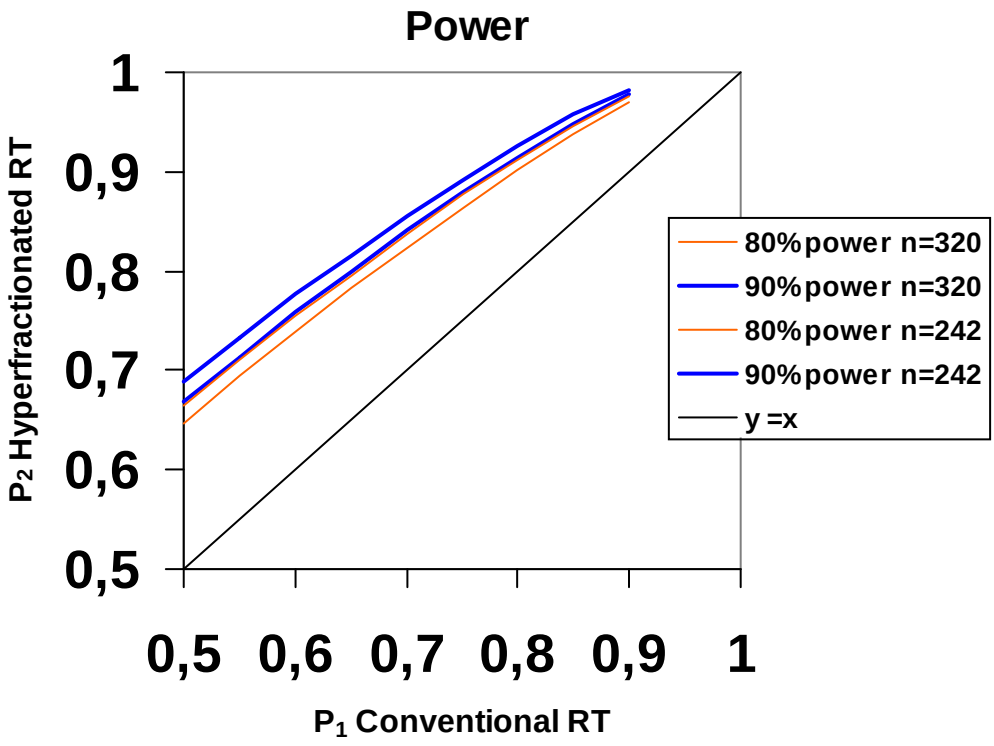
The per protocol analysis will exclude patients who have been randomised but who do not meet the eligibility criteria e.g. age, histology, staging, other malignant tumour disease etc. In addition, this analysis will exclude patients who do not meet eligibility criteria after central review (pathological, radiological and radiotherapy review) and patients who are not reviewed. Patients will also be excluded from per protocol analysis for the following reasons: patients who, do not receive any treatment at all, start RT more than 40 days after definitive surgery, do not meet RT quality assurance because of major deviations on RT treatment chart, receive less than 75% of the intended RT arm and thereafter are switched to the other arm, receive less than 90% of intended RT dose and patients who receive less than 4 cycles of chemotherapy with less than 80% of doses applied in each cycle. In the per

protocol analysis, if a patient is allocated to one arm and receives the other arm as treatment, analysis will be according to the treatment actually given.

13.10 Patient recruitment and power

The total recruitment time lasts until 31.12 2005. Thereafter a 2-year observation time follows. The study opened 01.01.2001. During the first 2 years approximately only HIT Group patients were included. From the start of the HIT- SIOP PNET 4 protocol patients from all participating countries, Austria, Belgium, Denmark, France, Germany, Italy, Norway, Spain, Sweden, Switzerland, The Netherlands and the United Kingdom will be included. Around 80 patients per year are estimated to be recruited during the last two years of the study. The number of patients lost to follow up will be regarded as negligible.

This study estimates a 3 year EFS of 70 % for patients in the standard RT arm and an expected EFS of 85 % for patients in the HFRT arm. The study should have a power of 90% to answer the main question. The total number of patients needed can be estimated as below. The study aims to recruit 320 patients.



P_1 denotes the calculated probability of 3 year event free survival of the conventional RT and P_2 the corresponding probability of the hyperfractioned RT. In most cases the assumed contribution of a patient to the comparison exceeds 3 years (for a few of them it could be 7 years). The log rank test compares the hazard functions of event for the two treatments during the study period but for the

convenience of interpretation the quantities P_1 and P_2 are used in the figure Two sizes, n=320 and n=242, are considered. The recruitment rate was assumed to be constant for 2.8 years at the level 33.6 patients per year and thereafter constant at the level 102.7 patients per year (the case n=320) and 67.3 patients per year (n=242), respectively. Furthermore it is assumed that the recruitment stopped after 5 years but the study continued 2 more years. The power was determined by simulation. The significance level was 0.040 and only the last occasion of analysis was considered. The hazard functions were assumed to be constant as functions of time, and no loss of follow up was assumed.

The curves 90% power n=320 almost coincided with 80% power n=242. For points (P_1, P_2) above the curve corresponding to 90% power, e.g., the power is higher than 90%. The line y = x corresponding to equal probabilities was drawn to facilitate the reading of the figure.

13.11 Results of the Biological Studies

The results of all biological studies will be collated centrally by Dr David Ellison, Northern Institute of Cancer Research, University of Newcastle upon Tyne, UK, but analysis of these results will depend upon the efficient exchange of data between Newcastle and the International Data Centre in Stockholm. This requires uniformity in the organisation of databases, which will be resolved by the start of the biological studies. The frequency and distribution of each of the molecular aberrations will be analysed. Their relationship to clinical and pathological features will be explored using standard Chi-square and Fisher test analysis. The impact of the presence of any given molecular aberration(s) on EFS and overall survival of patients will also be conducted using Log Rank univariate and Cox multivariate analyses.

13.12 Power calculation and statistical analysis of the neurological and endocrine follow-up

The results of all quality of survival studies, including the HUI, SDQ, endocrine and audiological data but excluding the quality of life (QoL) questionnaires, will be collated centrally by Dr Colin Kennedy at the University of Southampton. QoL questionnaire data will be collated by Dr Gabriele Calaminus at the University of Münster. Analysis of these results in Southampton (HUI, SDQ, endocrine and audiology) and Münster (QoL) will depend upon the efficient exchange of data between Southampton and Münster and between these centres and the International Data Centre in Stockholm. Dr Helen Spoudeas will supervise analysis of the endocrine data. This requires uniformity in the organisation of databases in the centres involved, which will be resolved by the start of the collection of quality of survival information.

The measures will provide a longitudinal, prospective description of Health Status and emotional health that is itself of value. However a primary aim is to compare the quality of outcome between the two treatment arms and hypotheses relate to an effect of treatment allocation on cognition, hearing, behaviour, growth and reproductive health.

Secondary Endpoints relating to Outcome

We aim to test the hypothesis that treatment allocation influences cognition, hearing, behaviour, growth and/or reproductive health. The size of the groups in each of the two treatment arms is planned to be 160 children. Assuming event free survival of 75 % and 10 % loss of these survivors to follow-up, the percentage difference between prevalence of outcomes among ascertained survivors in the two

treatment arms that the study would have 80 % power to detect at P<0.05 is:

Outcome in ascertained survivors (n=213)	Overall % prevalence (both arms)	% difference	Numbers affected (arm A and arm B)
Cognition impaired by 2 levels (HUI)	10	10	5 vs 16
Hearing loss 40dB at 4000Hz	10	10	5 vs 16
Cognition scored abnormal (HUI)	50	20	42 vs 64
SDQ score above screening threshold	50	20	42 vs 64
Growth failure	90	12	89 vs 102

For comparison of continuous variables such as the mean number of attributes scored as 'affected' (i.e.suboptimal) between the two treatment arms, transposition of the means and standard deviations reported in the study of French children with PNET [91] suggests that the HIT-SIOP PNET 4 study, with 106 ascertained surviving patients in each arm, would have the power to detect a mean difference of 0.6 between the numbers of attributes affected in the two treatment arms.

Analysis of binary outcome data will make use initially of chi-squared tests in order to compare the proportions of children with specific attributes in relation to baseline, treatment-related and demographic characteristics. Further analysis will make use of logistic regression techniques. When outcomes are ordinal (i.e. mild, moderate, severe) chi squared and chi-squared for trend tests will be used initially, and further analysis will make use of ordered polytomous regression techniques. For continuous outcomes variables initial analyses will make use of parametric, i.e. t-test, or non-parametric, i.e. Mann Whitney, as appropriate. Further analyses to explore the variability of outcome, possibly after suitable transformations will use multiple regression techniques.

14. Data Monitoring and Safety Committee (DMSC)

An independent DMSC composed of 3 international experts will monitor the progress of the trial on ethical and scientific backgrounds. The role of the DMSC will be:
- to review accrual rate
- to examine interim analyses

Each interim analysis will be reported to the DMSC.
- these interim analyses will remain confidential
- on the basis of these analyses, the DMSC will recommend whether the study can continue, or whether it should be changed or terminated prematurely.

To monitor toxicity:
- every 6 months the statistician for the trial will circulate a report to the members of the DMSC about toxicity. The DMSC will review these interim toxicity data and any relevant information will be forwarded to each Study Co-ordinator

- this biannual procedure is designed to prevent problems of major toxicity

To examine other trials:
- the DMSC will review reports of related studies performed by other groups or organisations to determine whether such information materially affects the aims or preliminary findings of the trial
- the DMSC will be asked to review any major modification to the study proposed by the Co-ordinators of the trial prior to its implementation

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Study Board

The Study Board will be primarily responsible for conduct of the trial. The board will receive and consider relevant communications from the International Data Centre and from the DMSC and thus be responsible for major decisions affecting running of trial.

The following individuals will sit on the Study Board:

Dr Birgitta Lannering

Dr Rolf Kortmann

Dr Barry Pizer

Dr Stefan Rutkowski

Dr Francois Doz

Dr Anders Oden

Dr Göran Gustafsson

National Trial Co-ordinators

France -	**Dr Francois Doz**
Germany -	**Stefan Rutkowski**
United Kingdom -	**Dr Barry Pizer**
Spain -	**Dr Aurora Navajas**
Italy -	**Dr Maura Massimino**
Nordic Countries -	**Dr Birgitta Lannering**
Belgium -	**Dr Stefaan Van Gool**
The Netherlands -	**Dr Roel Reddingius**

The National Trial Co-ordinators will have primary responsibility for the conduct of the study within their National Group and will also sit on the Study's Steering Group that will oversee the running of the study as a whole.
Each National Group will appoint a National RT Co-ordinator who will have primary responsibility for Radiotherapy issues within their National Group, and in particular will be responsible for the organisation of Radiotherapy Quality Control procedures.

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Appendix B

International Trial Co-ordination

The conduct of this study will be according to the following agreed procedures:

1. Status of Study

This is a collaborative study between a number of participating national groups. The co-ordinators for each group are listed above (Appendix A).

2. The Protocol

All national groups will use a common protocol for the international study except for HIT Group centres that will use the original HIT 2000 protocol with appropriate amendments in relation to the common study, HIT-SIOP PNET 4. The finalised master protocol in the English language will be held at the International Data Centre. Other national groups will be responsible for producing a literal translation in their own language.

Each national co-ordinator will be responsible for the distribution of protocols to centres within their national group via their national data centre as appropriate.

Appendices may be added independently by any of the national groups to address local needs, provided they have no bearing on the essential aims of the international protocol. However no change will be allowed to the eligibility criteria or the treatment procedures of the main protocol.

Subsequent to finalisation, the study chairman and the national co-ordinators must agree any amendments to the protocol.

3. Study Forms

One common set of forms will be used except for the HIT Group centres who will continue to use the HIT 2000 data forms. The master version (in English) of the study forms will be held at the International Data Centre. Each national co-ordinator will be responsible for distribution of forms to centres within his/her country (using their national data centre as appropriate). Additional forms may be produced independently by any national group for the collection of data additional to that required for the international study. Subsequent to finalisation, all national groups must agree amendments to the forms. The International Data Centre will be responsible for the issue of amended forms.

4. Data Collection

a) Each national group shall hold the master database for its own patients, and shall be responsible for data quality according to local practice.

b) The content of the database shall be identical to the data collected on the study core data forms.

c) The master database for the entire study will be held at the International Data Centre.

d) A complete data set will be transferred from each National Data Centre to the International Data Centre at least every six months.

e) Forms returned from the treating institutions shall be stored at the relevant National Data Centre.

f) Data transferred from the HIT database will be made compatible with the International Database.

5. Confidentiality of Patient Data

The use of names as patient identifiers on paper forms and on national databases will be according to national practice. An abbreviated patient identifier will be used for data transfer and for the master database.

6. Data Quality Control

On receipt of forms at the national data centre, common range and logical checks, agreed by the study co-ordinators, will be carried out on data prior to transfer to the master database. Any amendments to the checking programme will require mutual agreement of the study co-ordinators.

Data entry verification shall be carried out according to current national practice. Cross checks of data entry will be carried out occasionally, between national centres, on a sample of forms.

Data amendments shall only be carried out at the national data centre on the national database. Errors noted on the master database, after receipt of the group database, shall be reported back to the national centre.

Data audit of study forms against the patient record forms at the treating institution shall be performed to satisfy national requirements.

7. Data Analysis and Monitoring

Data will be released from the International Database to the Trial statistician responsible for interim analysis at given time intervals.

8. Serious Adverse Events - See section 12 – main text.

9. Treatment Stopping Rules for Individual Patients – See section 13.5 – main text.

10. Data Monitoring and Safety Committee (DMSC) – See section 14 – main text.

11. Central Review Processes

a) Chemotherapy Review

Chemotherapy forms shall be reviewed by the national group co-ordinator(s) and protocol deviations noted on the database. The review information shall be reported to the Trial coordinators.

b) Pathology Review - see Appendix D

c) Biological Studies - see Appendix E

d) Radiotherapy Review – see section 8.8

12. Follow Up Data

The National Data Centres will follow up all registered patients during and after completion of treatment according to the current protocol.

13. Institutional/Local Ethical Approval and Patient Consent

Institutional/local ethical approval will follow accepted national practice. National procedures for patient consent will be used.

14. Publication Policy

Participating centres may publish details of their own cases but will agree to allow the PNET 4 Committee exclusive rights to publish the results of PNET 4 study in part or in total. All such publications will be presented on behalf of the PNET 4 Committee and will acknowledge the contribution of the participating centres. Authorship of such publications will represent those members of the committee, and others who are involved in the preparation of the data and the manuscript. Authorship will be discussed with the full PNET 4 committee before preparation of publications (abstracts or manuscripts) and requires the approval of the Study Co-ordinators.

National working groups reserve their rights to publish their results separately after publication of the trial results with respect to the primary objectives. Data of the national explorative analyses will be shared and discussed within the group.

Appendix C

Neurosurgical Guidelines – Including Neurosurgical Data to be Collected

Pre-operative data.
The anatomical location of the tumour as seen on CT or MR will be recorded as well as the presence of any hydrocephalus, any cystic component and any intra-tumoural haemorrhage.

Intra-operative data and surgical technique.
The intended operative strategy will be recorded and whether the procedure was performed as an emergency or electively.

The neurosurgeon may use whatever means are felt clinically appropriate to control raised intracranial pressure and to relieve hydrocephalus prior or during the planned resection and this will be recorded.

The neurosurgeon will operate according to his/her own preferred method, using whatever high-technology adjuncts are felt appropriate.

The technology employed together with the availability of that technology will be noted. Any intra-operative limiting factors will be noted. The duration of the procedure 'skin-to-skin' will be recorded. The surgeon's contemporary intra-operative assessment of extent of resection will be noted, characterising it as gross total (no visible tumour) or partial resection (visible tumour).

Post-operative data.
The extent of resection will be assessed on CT or MR performed within 72 hours of surgery and categorised as gross total (CR), partial (PR), or unsure. Complications within 30 days of resection will be noted and categorised in a standardised fashion. The neurological state at around 30 days post-resection will be recorded according to the standardised format for pre-operative and for follow-up evaluations.

Second Look Surgery
As discussed in section 4.2.2, patients with residual disease of any size following surgery are eligible for inclusion into the PNET 4 trial. The Study Committee do, however, suggest that second look surgery be considered in patients with significant residual disease following primary surgery. The details of second look surgery will be recorded on the appropriate data form.

Lumbar CSF examination.
Post-operative lumbar puncture to obtain CSF for tumour cytology is an essential requirement as those patients with positive CSF cytology at Day 15 or later will be ineligible for this study. Lumbar puncture at Day 15 or after is therefore mandatory. The only exception is if an earlier lumbar CSF specimen has shown no malignant cells. It is therefore important that if lumbar puncture is performed for surgical reasons prior to Day 15 that an aliquot of CSF is sent to the neuropathologist for tumour cytology. If this examination is negative for tumour cells the patient will not need a further lumbar puncture for staging at Day 15. If this examination is positive for tumour cells the patient will still need a further lumbar puncture for staging at Day 15. The neurosurgeon must keep the oncologist appraised of the position. **Ventricular CSF is not an acceptable alternative to lumbar CSF for staging purposes.**

Appendix D

Neuropathology Guidelines

Objectives

1) Central review of pathology

   a) Confirmation of the (local) histological diagnosis of medulloblastoma / cerebellar PNET, with classification according to the WHO (2000) system.

b) Exclusion of non-eligible tumour types:
   Large cell medulloblastoma.
   Atypical teratoid rhabdoid tumour.
   Medulloepithelioma.
   Ependymoblastoma.

   Of the medulloblastoma variants listed in the WHO classification, the large cell medulloblastoma has a significantly poorer prognosis than the classic medulloblastoma, and is an indication for exclusion from the trial. However, if a local pathologist suspects this diagnosis, then this should be confirmed with the appropriate review pathologist as a 'fast-track' second opinion (see below).

2) Evaluation of the feasibility of providing central review of local pathological diagnoses before the start of adjuvant therapy.

3) Distribution of (paraffin wax embedded) tissue for approved biological studies.

Central review of pathology

Central pathology review will be requested on all patients entered into the study, and will be undertaken by a committee of 4 neuropathologists:

- David Ellison, Newcastle, UK (Neuropathology Co-ordinator)
- Torsten Pietsch, Bonn, Germany
- Dominique Figarella-Branger, Marseilles, France
- Marco Forni, Turin, Italy

In HIT Group centres, investigators will follow the HIT 2000 protocol, confirmation of local histological diagnosis being provided by the tumour reference laboratory in Bonn, generally before the start of adjuvant therapy.

Elsewhere, the working histological diagnosis will be provided by the local pathologist, but a tumour block and a copy of the pathology report should be submitted to the designated centre (see below) for pathological review as soon as possible after finalisation of the report. The feasibility of providing confirmation of the histological diagnosis, via the study registration centre, before the start of adjuvant therapy will be audited as part of this study. In this respect, pathological review will not aim to be retrospective, but ‘fast-track’, involving a close collaboration between local pathologist and (one)

central reviewer. The aim of this process is a mutually agreed histopathological diagnosis, but the final 'fast-track' decision on diagnosis and entry into the trial belongs to the local pathologist.

Dr. Figarella-Branger and Dr. Forni will undertake the central pathology review for centres in France and Italy respectively. Local pathologists in all other countries will submit tumour samples to Dr. Ellison in the UK.

The block of formalin fixed, paraffin wax embedded tumour should contain an adequate amount of tissue for both histological assessment and biological studies. All tissue blocks will be returned to the originating pathology department as soon as possible.

Neuropathology review will involve examination of standard histological preparations and, if required, immunohistochemistry to look for the expression of neuro-epithelial proteins (GFAP / synaptophysin / neurofilament protein / NEU-N), and of proteins that may be expressed by other tumours of the posterior fossa (cytokeratins / smooth muscle actin / desmin / epithelial membrane antigen), such as atypical teratoid / rhabdoid tumours. A Ki-67 labelling index will also be established using the MiB-1 antibody.

Appendix E

Biological Studies

For the first time in a SIOP study of central nervous system tumours, a series of biological studies will run alongside the clinical trial of CNS tumours.

Objectives

1. To test the principle that prospective biological studies can be successfully performed alongside a SIOP trial.

2. To examine the prognostic value of molecular abnormalities in PNETs in a large series of children treated according to a defined protocol.

The submission and use of tumour tissue for research will follow ethical guidelines of contributing EU countries. The distribution of tissue for these studies will be coordinated by the lead pathologist (Dr. Ellison), but facilitated through each of the laboratories run by members of the pathology committee (see schema).

Background

Despite the identification of oncogenes and tumour suppressor genes important in the progression of a variety of human cancers, including some brain tumours, relatively little is known about the molecular pathology of CNS PNETs. In particular, though a number of consistent karyotype abnormalities has been identified in PNETs, as have a small group of candidate oncogenes and tumour suppressor genes, an understanding of their biological / clinical significance is limited. The biological studies attached to PNET 4 trial will investigate the prognostic significance and other clinical associations of several molecular abnormalities previously identified in smaller more heterogeneous cohorts of PNET patients. In particular, they will investigate any relationship between specific molecular abnormalities and treatment response and clinical outcome, with the principal aim of identifying valuable prognostic markers for a more efficient patient stratification in future SIOP clinical trials. Furthermore, by recording the frequency and distribution pattern of these aberrations, both with regard to each other and other clinicopathological features, it is hoped that considerable insight will be gained into our understanding of PNET tumour biology. Finally, an important principle of the study is to demonstrate that collaborative research can be undertaken in the context of a SIOP trial across several countries in Europe.

Research studies

The following scientists will direct research studies attached to this trial:

Dr. D. Ellison, Northern Institute for Cancer Research, Newcastle-upon-Tyne, UK.
Dr. T. Pietsch, Dept. of Neuropathology, University of Bonn, Bonn, Germany.
Dr. M. Grotzer, Dept. of Paediatric Oncology, University of Zurich, Zurich, Switzerland.

The studies will have the following objectives:

1. To identify important molecular prognostic markers of use for routine disease risk stratification of children with clinically defined standard risk medulloblastoma. Molecular abnormalities investigated will include:

    a. Loss of 17p ± gain of 17q.
    b. Loss of 9q22.
    c. ErbB2 and ErbB4 receptor co-expression.
    d. *MYC* oncogene amplification / overexpression.
    e. Expression of TrkC.

1. To increase understanding of the role played by the interaction of these molecular aberrations in medulloblastoma disease behaviour and treatment responsiveness.

2. To establish the feasibility of performing multi-centre collection of fresh resected tumours for central RNA analysis using a room temperature storage protocol.

Scientific studies

Abnormalities of chromosome 17 and loss of 9q22

Deletions involving the short arm of chromosome 17 represent the most frequent genetic abnormality in medulloblastoma, occurring in 40 to 50% of primary tumours[66]. Though a number of studies in the literature have reported a significantly worse prognosis for patients whose tumours harbour deletions of 17p[67 68] this has not been a universal finding[69 70]. However, these studies have involved only small numbers of cases or combined a variety of techniques with different sensitivities to analyse 17p loss, thereby rendering them difficult to interpret. Loss of 17p is associated with gain of 17q, producing an isochromosome 17q i(17q), in a large proportion of medulloblastomas.

There is increasing evidence that the human homologue of *Drosophila* segment polarity gene *patched (PTCH)* may act as tumour suppresser in medulloblastoma. The possibility that deregulation of this system may result in malignant proliferation of granule cells and tumorigenesis was first suggested by the discovery that *PTCH* function is lost in Gorlin syndrome (GS), an inherited disorder associated with an increased risk of tumour development including medulloblastoma[71]. Following the localisation of the GS locus to 9q22.3-q31, two LOH studies identified deletion of this region not only in medulloblastomas derived from GS patients, but also in 5 of 33 sporadic tumours[72 73]. The gene responsible for GS was subsequently cloned and identified as *PTCH* (Hahn et al., 1996). Direct sequence analyses have since detected mutations in the *PTCH* gene in 12 out of a total of 97 sporadic medulloblastomas[75 76], and a close correlation between LOH at 9q22-q23, mutation of *PTCH* and the desmoplastic morphophenotype has been demonstrated [75].

Using an interphase FISH method on tumour nuclei extracted from paraffin wax embedded tissue, this study will test the hypotheses that loss of 17p, gain of 17q, i(17q) or a combination of these abnormalities is a prognostic marker for childhood PNETs and that loss of 9q22 is associated with a particular morphophenotype and biological behaviour.

ErbB receptor expression
In medulloblastoma, there appears to be a close relationship between the proportion of cells with elevated expression of ErbB2 and ErbB4 and high tumour mitotic index, advanced metastatic stage and reduced survival[78]. Using immunohistochemistry, this study will test the hypothesis that PNETs with a majority of ErbB2-positive cells demonstrate a more aggressive biological behaviour.

***MYC* oncogene amplification**
Available data suggest that around 6% of primary medulloblastomas harbour amplification of the *MYC* oncogene. Several studies have reported an adverse affect of *MYC* amplification on clinical outcome[67 79]. Further, evidence of an association between aggressive tumour behaviour and *MYC* amplification has been provided by Scheurlen *et al* [80], who reported a *MYC* amplification rate almost three times that observed in other studies (17%, n=5/29) in an analysis which included samples from clinically high risk patients. This study will examine *MYC* status using a combination of interphase FISH and qPCR.

mRNA Expression of TrkC and MYC
The family of neurotrophins has pleiotrophic effects on developing, mature and injured cells of the CNS[81]. Recently, two groups[82 83] have found that high TrkC mRNA expression is an independent predictor of a favourable clinical outcome in PNET patients in retrospective studies. By combining high TrkC expression and low MYC mRNA expression, the predictive power to identify a good-outcome group of medulloblastoma patients has been shown to be even greater[84]. This study will prospectively analyse TrkC and MYC mRNA expression in the trial's patients.

Management and Methods

Distribution of tumour tissue

The difficulties in obtaining and transporting fresh tissue from referral centres to central research laboratories are recognised, and that to be clinically useful and widely applicable, molecular prognostic markers need to be measurable using relatively simple and routine methodologies. Therefore, with the exception of TrkC mRNA expression, all analyses in the proposed study will be performed on formalin fixed, paraffin wax embedded (FFPWE) material, distributed from the coordinator's neuropathology reference laboratory (UK).

In order to ensure the most efficient and standardised use of FFPWE material, a FFPWE tumour block should be forwarded by the local neuropathology laboratory to one of the central study neuropathologists, according to the schema for referral of tumour for central pathological review and biological studies. In Germany, France and Italy, central laboratories will cut sections for pathological review, and then submit the FFPWE block to Dr. Ellison in Newcastle, who will arrange distribution of tissue to the appropriate research groups. This will ensure that each block is sectioned on only one or two occasions, avoiding any waste of material through repetitive 'trimming'.

Only material specified in this document will be removed from the blocks, which will then be returned immediately to the referring centre. If material in the block is limited then collection of tissue will be

prioritised to ensure that all returned blocks retain material for future histopathological use by the referring centres.

Special case - TrkC and MYC mRNA analysis

There are currently no reliable immunoreagents available for the analysis of TrkC expression in tumour biopsies. Therefore, its assessment requires analysis of RNA. Previously, this has required the collection, storage and transport of snap-frozen fresh biopsy samples. However, this approach is cumbersome and not feasible for large multi-centre prospective studies.

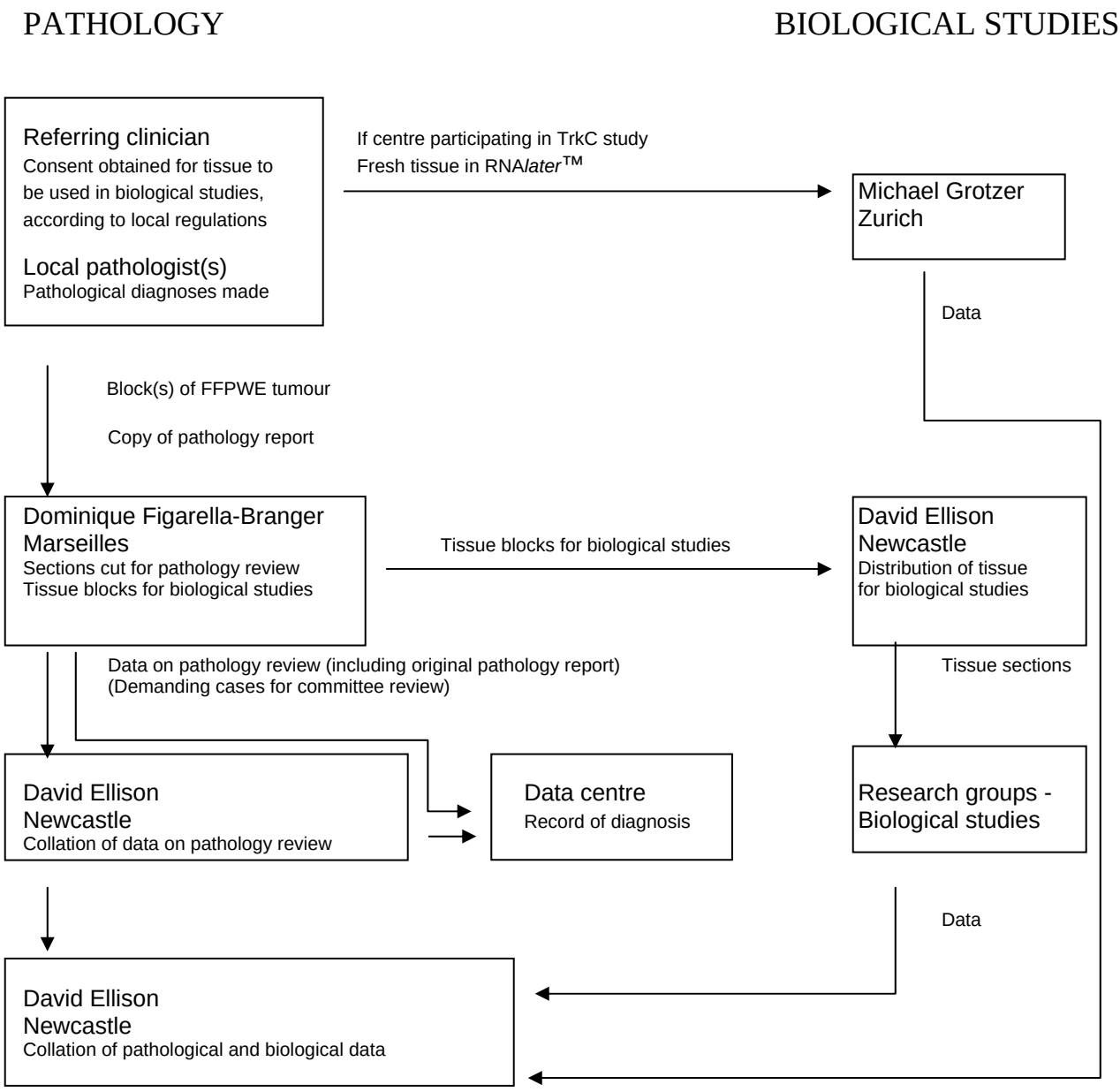
An alternative method of preserving tissue samples for subsequent RNA analysis is storage in RNA*later*™. This novel RNA stabilization solution contains proprietary reagents that rapidly penetrate fresh tissue and deactivate RNAases, and high quality RNA can be prepared from tumour tissue stored at room temperature. Short-term storage and shipment of well-preserved tumour tissue is clearly feasible for all institutions, thereby facilitating large multi-centre studies of molecular markers.

This collection protocol will be piloted in a number of European centres to assess the feasibility of RNA collection both as part of PNET 4. Centres interested in the TrkC mRNA study are highly welcome. Please contact Dr. Michael Grotzer (Michael.Grotzer@kispi.unizh.ch). Thus, not all centres will be required to participate in this aspect of the study.

All centres participating in the TrkC/MYC mRNA study will receive transport sets of tubes filled with RNAlater and shipment guidelines.

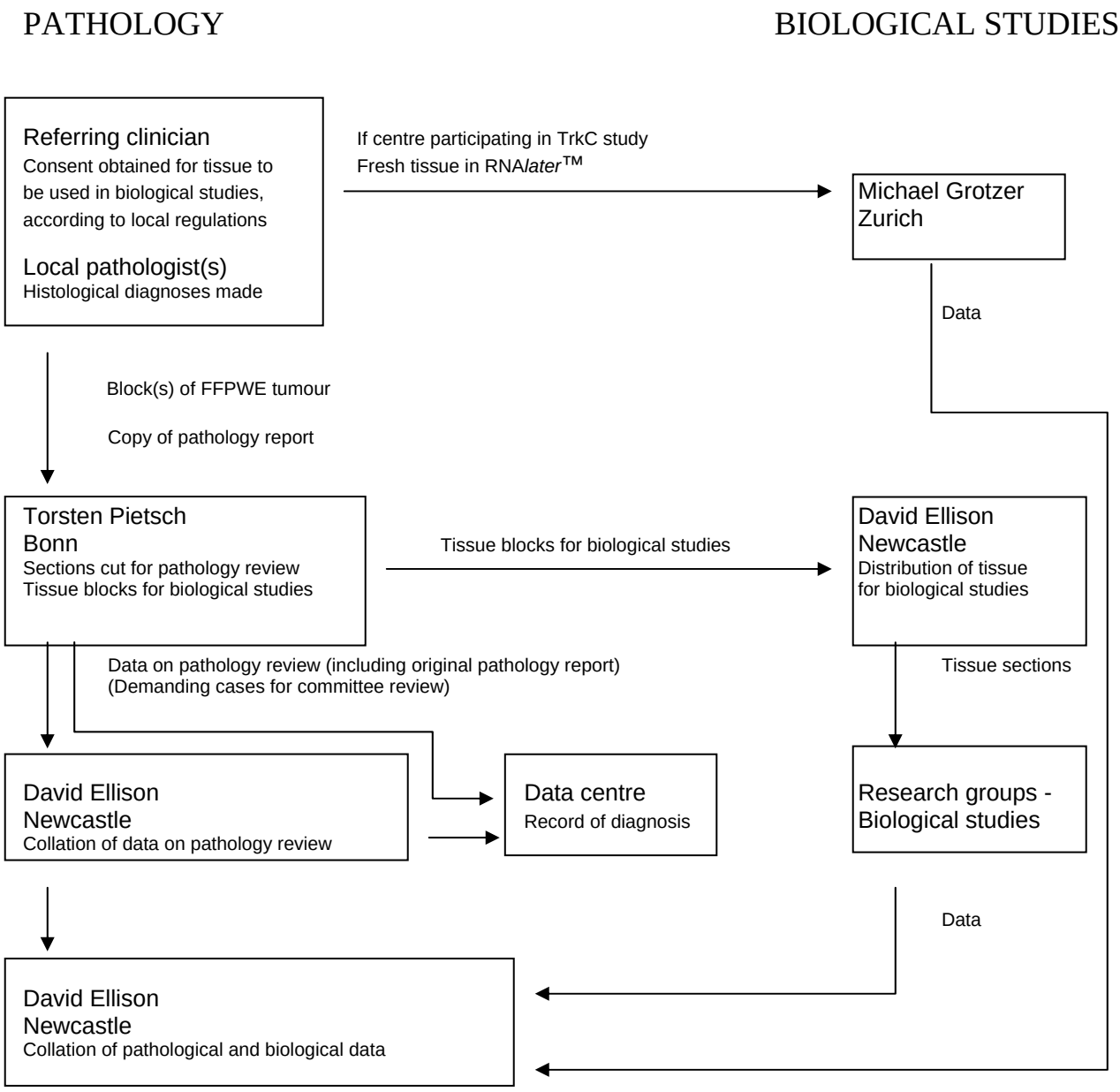
SCHEME FOR PATHOLOGY REVIEW AND BIOLOGICAL STUDIES

CENTRES IN FRANCE



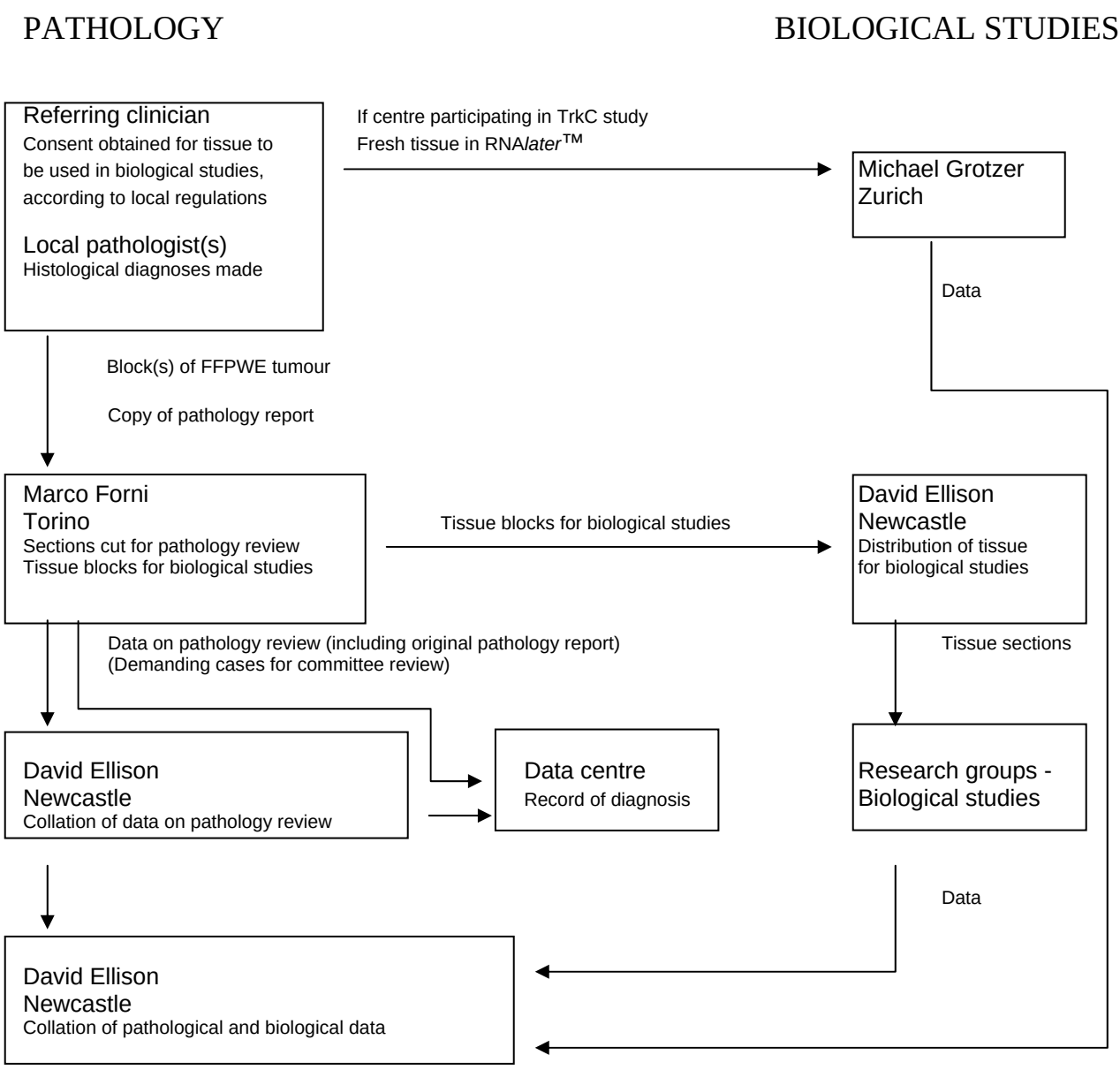
SCHEME FOR PATHOLOGY REVIEW AND BIOLOGICAL STUDIES

CENTRES IN GERMANY, AUSTRIA AND SWITZERLAND



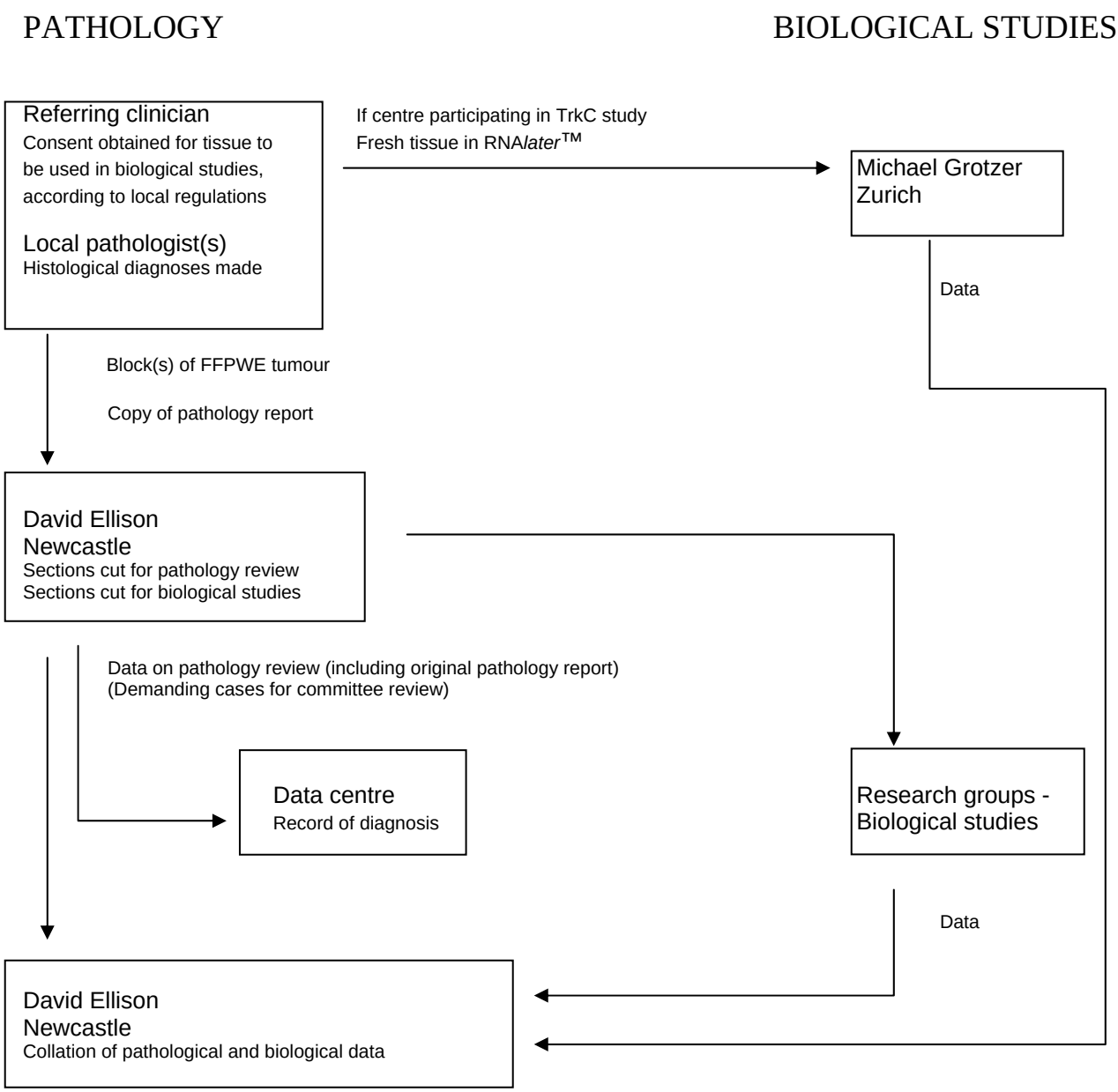
SCHEME FOR PATHOLOGY REVIEW AND BIOLOGICAL STUDIES

CENTRES IN ITALY



SCHEME FOR PATHOLOGY REVIEW AND BIOLOGICAL STUDIES

ALL CENTRES OUTSIDE FRANCE, GERMANY, AUSTRIA, SWITZERLAND & ITALY



Appendix F

Cytopathology guidelines

Cytological analysis of CSF for assessment of M1 status.

This will be provided by a local cytopathologist.

Central review of cytological preparations of CSF is recommended but not mandatory. This will be at the discretion of individual National Groups.

It is recommended that at least 2ml of CSF be supplied for cytological examination. This quantity will allow the preparation of several slides, and the use of immunocytochemistry if required. Cytospin preparations should be made as soon as possible after lumbar puncture to ensure preservation of cytological features.

Involvement of CSF pathways by tumour is defined as the unequivocal identification of primitive neuroectodermal cells in lumbar CSF (analysis of ventricular CSF is not appropriate for the PNET 4 study), either on cytological grounds or with a combination of cytological and immunocytochemical features (e.g. reactivity for GFAP or a neuronal marker, such as synaptophysin).

Appendix G

Neuroradiology Guidelines and Radiology Quality Control

The following Neuroradiology Guidelines apply to all National Groups.

Radiology Review Procedures will be conducted on a National basis according to a Nationally approved protocol although a common set of Radiology Review Data forms will be used.

Neuroradiology Guidelines

A) MRI - Brain imaging

Sequences:

- Whole brain axial T1 SE, whole brain axial T2 SE/TSE
- Post contrast axial T1 SE, additional plane (sagittal and/or coronal).
- Control MRIs should be comparable to each other and to pre and postoperative MR examinations.
- Pre- and post contrast imaging must employ the same scan and slice positions.

Parameters:

- Slice thickness: 5 mm or less.
- Matrix: 256 x 256 (effective)
- Scan plane: axial bicommisural.
- Slice gaps of more than 10% should be avoided.
- T1-weighted Gradient echo sequences (except additional) should be avoided.

Contrast:

- Intravenous (i.v.) Gadolinium DTPA: 0.1 mmol/kg (= 0.2ml/kg) bodyweight. (or an equivalent Gadolinium contrast medium)
- An i.v. line should be placed prior to attending the MR department.

B) Spinal axis imaging

Sequences:

Post contrast whole spine (at least down to S2) sagittal T1-weighted SE.
Additional axial T1-SE images of suspicious or obvious meningeal dissemination or of the conus and epiconus region if perimedullary vessels appear prominent or confusing.

Axial sequences of suspicious or obvious meningeal dissemination.

Parameters:

Slice thickness 3mm or less for the sagittal sequence. Slice thickness for the axial sequence optional.

Contrast:

The spinal examination may be performed immediately after the cranial MRI. Time elapse between contrast application and imaging of more than 45 minutes must be avoided. If performed separately follow the guideline for the cranial MRI examination.

C) Cranial CT:

Posterior fossa:

4 mm thick or less contiguous slices. Avoid direct irradiation of the eye lens.

Supratentorial brain:

8-10 mm thick contiguous slices covering the whole of the remaining intracranial compartment.

- CT should be performed prior and after slow i.v. administration of a non-ionic iodinated contrast medium (2mg/kg body weight) employing identical slice thickness and position.
- Intravenous access should be obtained prior to attending the CT department.

Radiology Quality Control

PNET 4 is designed for standard risk patients and thus careful staging is a fundamental entry requirement for the study. A high standard of neuroradiology both technically and in terms of image interpretation is required. This particularly applies to this study where reduced dose radiotherapy is utilised which may significantly compromise the outcome of high-risk patients that are misdiagnosed as standard risk patients.

- Quality control (QC) of neuroradiology is considered a fundamental component of the PNET 4 study.

- Neuroradiology QC will be organised and undertaken on a national basis.

- A National Neuroradiology QC Coordinator will be appointed by each National Group. This Coordinator will work in close corporation with named radiology colleagues forming the National Neuroradiology QC Panel. This will ensure the constant availability of a QC assessor without delay. All relevant cranial and spinal imaging at diagnosis will be submitted for QA.

- Although not mandatory, some national groups may wish to undertake pre-radiotherapy QC to ensure that patients who are not standard risk receive appropriate radiotherapy.

- It is recommended (although not mandatory) that radiology QC be undertaken prior to the end of radiotherapy. This is again to ensure that patients with metastatic disease on QC can receive modification of their radiotherapy treatment.

- For all patients, neuroradiology QC must be undertaken within 1 year of diagnosis (if not performed at an earlier stage).

- The National Neuroradiology QC committees will provide a report, at least on an annual basis to the National Study Coordinator who will in turn inform the International Data Centre.

All National Neuroradiology committees will use a common proforma for neuro-radiology QC. Countries who do not wish to set up their own QC panel should, at the start of the study, identify the QC panel of a National Group of their choice, which will provide the QC for them.

UK Radiology Quality Control

The UK Neuroradiology Coordinator (Dr Tim Jaspan – appendix A) together with the UK PNET 4 Trial Coordinator (CRCTU Data Centre) will coordinate Neuroradiology QC in the UK.

A common PNET 4 Radiology Quality Control proforma will be adopted.

Although not mandatory, all clinicians recruiting patients to PNET 4 will be invited to submit their patient's diagnostic (whole neuraxial) and post-operative (cranial) imaging for prospective Neuroradiology QC. This should be undertaken preferably within a week of the start of radiotherapy. A

full set of duplicate images of the diagnostic and post-operative (ideally not copies – although these are acceptable) should be made and sent to the Trial Coordinator.

For prospective evaluation, the Trial Coordinator will then send the imaging to the most appropriate member of the UK Neuroradiology QC panel for evaluation. The radiology QC form will be used for the evaluation, which will then be sent back to the CRCTU centre by e-mail, the patient details being encrypted.

Diagnostic imaging for all UK patients entered into the PNET 4 trial will be retrospectively reviewed by the Neuroradiology panel on an annual basis, with a minimum of three Neuroradiologists undertaking the review.

The UK Neuroradiology review panelists:

Dr Tim Jaspan
Dr Neville Wright
Professor Paul Griffiths
Dr Neil Stoodley
Dr Juliet Britton

Appendix H

Recommended Guidelines for the Administration of Cisplatin (UK VERSION)

T = 0 hours
Pre-hydration:

- 3 hours pre-hydration with 2.5% dextrose/0.45%saline at 200mls/m^2/hr
- Run fluid at 200mls/m^2/hr (total volume 600ml/ m^2, no maximum)

NB: It is critical to establish and maintain a good urine output prior to cisplatin administration. Therefore monitor urine output hourly and if urine output falls below 3ml/kg/hr for 2 hours give a bolus of mannitol 0.5g/kg over 15 to 30 minutes and additional fluid of 10ml/kg 2.5% dextrose/0.45% saline. DO NOT use frusemide as this may impair renal cisplatin clearance.

T = 3 hours
Hydration during and until 6 hours post Cisplatin (i.e. infuse over 12 hours)

- 2.5% dextrose/0.45% saline
- Plus 6g mannitol per 500ml
- Plus 10mmol potassium chloride per 500ml
- Run fluid at 125mls/m^2/hr (total volume 1500ml/ m^2, maximum volume 2250ml)

Hydration should be in a separate bag from the cisplatin and the two can either run through separate lines of a double lumen central line or can be connected by a Y-junction into a single line.

T = 3 hours
Cisplatin infusion over 6 hours:

- Cisplatin 70 mg/m^2 in 0.9% saline over 6 hours
  Suggested volume of 0.9% saline for infusion:
  <50mg in 100ml
  50 to 100mg in 150ml
  >100mg in 250ml

T = 15 hours
Hydration for subsequent 18 hours (i.e. until 24 hours after the end of cisplatin infusion)

- 2.5% Dextrose/0.45% saline
- Plus 10mmol potassium chloride per 500ml
- Plus 5mmol Mg sulphate per 500ml
- Plus 0.3mmol Ca gluconate per 500ml
- Run fluid at 125mls/m^2/hr (total volume 2250ml/ m^2, maximum volume 3375ml)

Appendix I

Drug Information

UKCCSG Drug Monographs

1. Cisplatin

Alternative Names:
- Cis DDP
- Cis diamminedichloro-platinum

Mechanisms of action:
- Produces interstrand and intrastrand DNA crosslinks.

Considerations prior to chemotherapy

- Audiology
- Renal function
- Adequate hydration and diuresis must be established prior to administration
- FBC

Adverse Effects

Common
- Nausea/vomiting (may be delayed)
- Nephrotoxicity (dose limiting)
- Myelosuppression
- Hypokalaemia
- Hypomagnesaemia
- Hyperuricaemia
- Alopecia

Occasional
- Peripheral neuropathy
- Taste disturbance

Rare
- Anaphylaxis
- Other neurotoxicity
- Ototoxicity
- Ocular

Interactions
- Co-administration with potentially nephrotoxic agents should be avoided due to the risk of acute reductions in GFR and hence decreased clearance, as well as additive renal toxicity.
- Concomitant administration of cisplatin and etoposide may reduce etoposide clearance.

Overdosage
- Full supportive measures should be considered
- Plasmapheresis may be of use in cisplatin overdosage

Dilution specification and stability:
- Cisplatin is stable in Sodium Chloride 0.9% for 7 days
- It remains stable in Sodium Chloride 0.9% in the presence of magnesium sulphate & potassium chloride for up to 24 hours
- Do not refrigerate
- No need to protect from light

NB. The minimum concentration of sodium chloride providing an acceptable level of stability is approximately 0.3% w/v

2. Vincristine

Alternative names
- Oncovin

Mechanisms of action
- Tubulin binding agent producing mitotic arrest.

Considerations prior to administration
- Well established, robust, venous access.
- Neurotoxicity

Adverse effects

Common
- Alopecia
- Abdominal pain - cramps
- Pain in jaw, bones and joints
- Constipation

Occasional
- Peripheral neuropathy (loss of deep tendon reflexes)
- Autonomic neuropathy (paralytic ileus, urinary retention)

Rare
- Leucopaenia, Thrombocytopaenia, Anaemia
- Nausea and vomiting
- Raised LFTs (mild and transient)
- Convulsions
- Diplopia and Photophobia

Toxicity related to individual and cumulative dose of Vincristine

Recommended routes
By bolus injection or into the tubing of a fast-running intravenous infusion. Hydration not required.

CAUTION

Vincristine is a highly vesicant drug, and great care must be taken to avoid extravasation.

DO NOT GIVE INTRATHECALLY

Dose /schedule
- Variable
- Dose reduction may be necessary if toxicity unacceptable
- The need to limit the total vincristine dose per administration to 2mg is not supported by clinical experience in adults.

Interactions
Vincristine plasma clearance can be reduced by nifedipine, cimetidine or ranitidine, and increased by phenobarbitone. The clinical relevance of these interactions in not clear.

Overdose
Plasmapheresis and phenobarbitone have been reported to be of value in cases of systemic vincristine overdose.

Dilution specification
- Dextrose 5%, Sodium Chloride 0.9%
- Undiluted at 1 mg/ml but at this concentration there would be increased toxicity with extravasation, therefore can be administered at lower concentrations, e.g. 0.2 mg/ml.

Stability
- Solution 1 mg/ml - 2 years in vial at 2 to 8 ^{o}C
- Lyophilised powder - 3 years at 2 to 8 ^{o}C. Chemically stable for 30 days after reconstitution when stored at 2 - 8 ^{o}C.

3. Carboplatin

Alternative names
- JM8
- Paraplatin (Proprietary Name**)**
- CBCDA

Mechanism of action
Produces interstrand and intrastrand DNA crosslinks

Considerations prior to administration
- Renal function
- FBC

Adverse effects

Common
- Nausea + vomiting
- Myelosuppression
- Persisting thrombocytopenia

Occasional
- Ototoxicity
- Raised LFT's (Alk Phos)
- Nephrotoxicity

Rare
- Neurotoxicity
- Rash
- Anaphylaxis + anaphylactoid reactions
- Ocular, transient visual disturbances
- Alopecia

Recommended routes
Intravenous

Administration:
Administered as a intravenous infusion over 1 hour or greater if dictated by fluid volume

Interactions
Co administration with potentially nephrotoxic agents should be avoided due to the risk of acute reductions in GFR and hence decreased drug clearance.

Overdose
- Full supportive measures, including the use of growth factors should be considered.
- Carboplatin is removed by haemodialysis. Although there are no publications on its use following overdosage, haemodialysis would be a reasonable management option.

Dilution specification & stability
- Dextrose 5%
- Concentration is not critical and should be adjusted to the child's fluid requirements
- Carboplatin can be diluted as low as 500 micrograms/ml
- Hydration is not required
- Once reconstituted, carboplatin is stable for 8 hours at room temperature, or 24 hours if refrigerated

Pharmacokinetics
Carboplatin is eliminated primarily by urinary excretion.

4. Lomustine (CCNU)

Considerations prior to administration

- Full blood count
- Liver function
- Renal function

Adverse effects

Common

- Myelosuppression
- Anorexia, nausea and vomiting
- Alopecia

Occasional

- Mucosal ulceration
- Transient liver function abnormalities

Rare

- Pulmonary infiltrate and fibrosis
- Progressive renal impairment

Dosing of Lomustine

The availability of lomustine in 10, 40 and 100mg capsules affects the ability to dose accurately especially in young patients. Simply rounding up or down to the nearest 10 mg results in variance in dosing which can be as high as 20%. To achieve a more consistent result please refer to the dosing table (Appendix J) which indicates doses resulting in the smallest absolute percentage change from the calculated ideal dose. In most instances this will be +/-10% of the ideal dose. For patients whose surface area fall between those noted in the table round off to the nearest 10mg that results in the smallest absolute percentage change.

Recently in the UK the 10 mg capsule has been discontinued but can be imported via IDIS on a named patient basis.

Appendix J

Lomustine (CCNU) Dosing

Surface Area	Ideal Dose	Actual Dose to be given	Variance (%) from ideal
2.0	150	150	0
1.90	143	140	-2
1.80	135	130	-4
1.70	128	130	+2
1.60	120	120	0
1.50	112	110	-2
1.40	105	100	-5
1.30	98	100	-2
1.20	90	90	0
1.10	82	80	-3
1.00	75	80	+7
0.95	71	70	-1
0.90	68	70	+4
0.85	64	60	-6
0.80	60	60	0
0.75	56	60	+7
0.70	53	50	-5
0.65	49	50	+2
0.60	45	40	-11
0.55	41	40	-2
0.50	38	40	+6

Note: For patients whose surface area falls between those noted in the table, give a dose that results in the smallest absolute change from the ideal dose. A similar method should be used for calculating dose reductions, i.e., rounding off the nearest 10 mg dose that results in the smallest absolute change.

Appendix K

Schwartz Formula for Estimation of Creatinine Clearance (Ccrea)

1) For [creatinine] in mg/dL

$$C_{(crea)}\ (ml/min/1.73m^2) = \frac{F \times Length\ (cm)}{Plasma\ Creatinine\ (mg/dL)}$$

Where **F** is proportional to body muscle mass, hence depending on age and gender:

Male, 3 – 16 years F = 0.55
Female, 3 – 16 years F = 0.55
Male, 16 – 21 years F = 0.70

2) For [creatinine] in umol/L

$$C_{(crea)}\ (ml/min/1.73m^2) = \frac{F \times Length\ (cm)}{Plasma\ Creatinine\ (umol/L)}$$

Where **F** is proportional to body muscle mass, hence depending on age and gender:

Male, 3 – 16 years F = 49
Female, 3 – 16 years F = 49
Male, 16 – 21 years F = 62

Reference: Schwartz GJ, Brion LP, Spitzer A. The use of plasma creatinine concentration for estimating glomerular filtration rate in infants, children and adolescents. *Pediatr Clin North America* 1987; 34: 571-590.

Appendix L Common Toxicity Criteria

Shortened listing of National Cancer Institute Common Toxicity Criteria (CTC), Version 2.0

Created October 2001

This abbreviated version of the NCI Common Toxicity Criteria catalogues the most usual problems seen during treatment for childhood cancers. However it is not exhaustive and if you suspect a drug toxicity that is not listed the full listing can be obtained via the CTEP Home Page (http://ctep.info.nih.gov). This site also carries a manual for using the coding system.

Two categories of toxicities should be separately recorded when reporting the toxicity results of the treatment: acute or subacute, and chronic or long-term toxic effects.

Separate criteria are available for coding of late radiation effects – RTOG/EORTC Late Radiation Morbidity Scoring Scheme, Appendix IV of CTC Version 2.0 – contact CRCTU Data Centre for information.

WNL = within normal limits

LLN = Lower limit of normal values.

ULN = Upper limit of normal values.

GENERAL PERFORMANCE					
CRITERIA	**Grade 0**	**Grade I**	**Grade II**	**Grade III**	**Grade IV**
Lansky or Karnofsky	> 90 - 100	90 to > 70	70 to > 50	50 to > 30	< 30
WHO Scale	Capable of all normal activities	Capable of light activities except all laborious physical activities	Ambulant and capable of self-care but incapable of all other activities. Not resting or sitting more than 50% of waking hours	Capable of some personal activities but confined to a bed or chair more than 50% of waking hours	Confined totally to a bed or chair, incapable of all activities, even essential activities such as eating
BODY WEIGHT (Loss or gain from baseline)	< 5.0 %	5.0 - 9.9%	10.0 - 19.9%	> 20%	-

HEMATOLOGICAL					
TOXICITY	**Grade 0**	**Grade I**	**Grade II**	**Grade III**	**Grade IV**
Haemoglobin	WNL	<LLN - 100 g/L <LLN – 10.0 g/dL	80 to 100 g/L 8.0 to 10.0 g/dL	65 to 79 g/L 6.5 to 7.9 g/dL	< 65 g/L < 6.5 g/dL
WBC: x10 ^{9}/L	>4.0	3.0 - 3.9	2.0 - 2.9	1.0 - 1.9	< 1.0
Neutrophils: x10 ^{9}/L	> 2.0	1.5 - 1.9	1.0 - 1.4	0.5 - 0.9	< 0.5

Platelets: x10 $^{9}/_{L}$	WNL	<LLN - 75	≥ 50 to 74.9	≥ 10 to 49.9	< 10
Haemorrhage	NONE	Mild no transfusion	-	Requiring transfusion	Catastrophic bleeding requiring major non-elective intervention.

COAGULATION Note: See the HaEMORRHAGE category for grading the severity of bleeding events.

TOXICITY	**Grade 0**	**Grade I**	**Grade II**	Grade III	**Grade IV**
Partial thromboplastin time (PTT)	WNL	>ULN - ≤1.5 x ULN	>1.5 - ≤2 x ULN	>2 x ULN	-
Prothrombin time (PT)	WNL	>ULN -≤1.5 x ULN	>1.5 - ≤2 x ULN	>2 x ULN	-
Fibrinogen	WNL	≥ 0.75 - < 1.0 x LLN	≥0.5 - < 0.75 x LLN	≥0.25 - < 0.5 x LLN	<0.25 x LLN
Disseminated Intravascular Coagulation (DIC) Also consider Platelets.	Absent	-	-	Laboratory findings present with **no** bleeding	Laboratory findings **and** bleeding

Note: Must have increased fibrin split products or D-dimer in order to grade as DIC.

Thrombotic Microangiopathy (e.g., thrombotic thrombocytopenic purpura/TTP or hemolytic uremic syndrome/HUS)	Absent	-	-	Laboratory findings present without clinical consequences	Laboratory findings and clinical consequences, (e.g., CNS hemorrhage/ bleeding or thrombosis/ embolism or renal failure) requiring therapeutic intervention

Note: Must have microangiopathic changes on blood smear (e.g., schistocytes, helmet cells, red cell fragments)

CARDIAC

TOXICITY	**Grade 0**	**Grade I**	**Grade II**	Grade III	**Grade IV**
(DYS) Rhythm	None	Asymptomatic, transient, requiring no therapy	Symptomatic, but requiring no therapy	Symptomatic and requires treatment	Life threatening (E.g. arrhythmia associated with CHF, hypotension, syncope, shock)
Cardiac Left Ventricular Function	No change	Asymptomatic, decline of resting LVEF < 20% of baseline	Asymptomatic, decline of resting LVEF > 20% of baseline	Mild CHF responsive to therapy	Severe or refractory CHF (congestive heart failure)
Cardiac Echography: Fractional Shortening	Normal	>25% to ≤ 30%	>20% to ≤ 25%	> 15% to ≤ 20% Mild CHF responsive to therapy	≤ 15 % Severe or refractory CHF (congestive heart failure)

TOXICITY	Grade 0	Grade I	Grade II	Grade III	Grade IV
Cardiac Ischaemia	None	Non specific T- wave flattening or changes.	Asymptomatic, ST and T - wave changes suggesting ischaemia	Angina without evidence for infarction.	Acute myocardial infarction
Pericardial Effusion / Pericarditis	None	Asymptomatic, effusion, no intervention required	Pericarditis (rub, chest pain, ECG changes)	Symptomatic effusion, drainage required	Tamponade; drainage urgently required
Hypotension	None or No change	Changes requiring no therapy(including transient orthostatic hypotension)	Requiring brief fluid replacement or other therapy but not hospitalisation: no physiological consequences	Requiring therapy and sustained medical attention, but resolves without persisting physiological consequences	Shock (associated with acidemia and impairing vital organ function due to tissue hypoperfusion)
Hypertension*	None or no change	Asymptomatic, transient increase > 95th percentile of ULN	Recurrent/persistent increase > 95th percentile of ULN Not requiring treatment	Requires therapy or more intensive therapy than previously	Hypertensive crisis

* For paediatric patients use age & sex appropriate normal values to give >95th percentile of Upper Normal Limit (ULN)

Acute Vascular Leak Syndrome	Absent	-	Symptomatic, but not requiring fluid support.	Respiratory compromise, or requiring fluids.	Life threatening; requiring pressor support and/or ventilatory support.

CONSTITUTIONAL SYMPTOMS

TOXICITY	Grade 0	Grade I	Grade II	Grade III	Grade IV
Fatigue (lethargy, malaise, asthenia) Note: See page 1 for performance status scales.	None	Increased fatigue over baseline, but not altering normal activities	Moderate (e.g., decrease in performance status by 1 WHO/ECOG level or 20% Karnofsky or Lansky) or causing difficulty performing some activities	Severe (e.g., decrease in performance status by $\geq$ 2 ECOG levels or 40% Karnofsky or *Lansk*y) or loss of ability to perform some activities	Bedridden or disabling
Rigors, chills	None	Mild, requiring symptomatic treatment (e.g., blanket) or non- narcotic medication	Severe and/or prolonged, requiring narcotic medication	Not responsive to narcotic medication	-
Sweating (diaphoresis)	Normal	Mild and occasional	Frequent or drenching	-	-

INFECTIONS / FEVER

TOXICITY	Grade 0	Grade I	Grade II	Grade III	Grade IV
Infection	None	Mild, no active treatment	Moderate, loacised infection requiring local or oral treatment.	Severe, systemic infection, requiring IV antibiotic or antifungal teatment, or hospitalisation	Life Threatening Sepsis (e.g. septic shock)
Fever in absence of infection	None	38.0 – 39.0 ^{o}C	39.1 – 40.0 ^{o}C	> 40.0 ^{o}C for < 24 hours	> 40.0 ^{o}C for > 24 hours or with hypotension

DERMATOLOGY / SKIN					
TOXICITY	**Grade 0**	**Grade I**	**Grade II**	**Grade III**	**Grade IV**
Allergy	None	Transient rash, drug fever < 38°C	Urticaria, drug fever ≥ 38°C Asymptomatic bronchospasm	Symptomatic bronchospasm requiring parenteral medication, +/- urticaria; allergy-related oedema/angioedema	Anaphylaxis
Injection site reaction	None	Pain or itching or erythema	Pain or swelling, with inflammation or phlebitis	Ulceration or necrosis that is severe or prolonged, or requiring surgery	-
Rash / Desquamation	None or no change	Scattered macular or papular eruption or erythema: asymptomatic.	Scattered macular or papular eruption with pruritus or other associated symptoms covering less than 50% of body surface. Or localised desquamation or other lesions covering < 50% of body surface.	Generalized symptomatic macular, papular or vesicular eruption Or desquamation covering ≥ 50% of body surface.	Generalised exfoliative or ulcerative dermatitis
Erythema Multiforme (e.g.,Stevens-Johnson syndrome, Toxic epidermal necrolysis)	Absent	-	Scattered, but not generalized eruption	Severe or requiring IV fluids (e.g., generalized rash or painful stomatitis)	Life-threatening (e.g., exfoliative or ulcerating dermatitis or requiring enteral or parenteral nutritional support)
Alopecia	No loss	Mild hair loss	Pronounced or total hair loss	-	-

GASTROINTESTINAL					
TOXICITY	**Grade 0**	**Grade I**	**Grade II**	**Grade III**	**Grade IV**
Stomatitis	None	Painless ulcers, erythema, or mild soreness	Painful erythema, oedema, or ulcers, but can eat or swallow	Painful erythema, oedema, or ulcers requiring IV hydration.	Requires parenteral or enteral support or prophylactic intubation
Nausea	None	Able to eat reasonable intake	Intake significantly decreased but can eat	No significant intake, requiring IV fluids.	-
Vomiting	None	1 episode in 24 hours	2 - 5 episodes in 24hrs	≥ 6 episodes in 24 hrs; or need for IV fluids	Requires parenteral nutrition; or physiologic consequences requiring intensive care: or haemodynamic collapse.
Diarrhoea	None	Increase <4 stools/day over pre-treatment	Increase 4 - 6 stools/day or nocturnal stools.	Increase ≥7 stools/day or incontinence or need for parenteral support for dehydration	Physiologic consequences requiring intensive care: or haemodynamic collapse.
Anorexia	None	Loss of appetite	Oral intake significantly decreased	Requiring IV fluids	Requiring feeding tube or parenteral nutrition

TOXICITY	Grade 0	Grade I	Grade II	Grade III	Grade IV
Colitis	None	-	Abdominal pain with mucus and/or blood in stool	Abdominal pain, fever, change in bowel habits with ileus or peritoneal signs, and radiographic or biopsy documentation	Perforation or requiring surgery or toxic megacolon
Pancreatitis	None	-	-	Abdominal pain with pancreatic enzyme elevation	Complicated by shock (acute circulatory failure)
Constipation – see also **NEUROLOGICAL** Ileus (or neuroconstipation)	None	Requiring stool softener or dietary modification	Requiring laxatives	Intractable constipation requiring manual evacuation or enema	Obstruction or toxic megacolon

HEPATIC					
TOXICITY	**Grade 0**	**Grade I**	**Grade II**	**Grade III**	**Grade IV**
Bilirubin	WNL	< 1.5 x ULN	1.6 to 3.0 x ULN	3.1 to 10.0 x ULN	> 10.0 x ULN
Transaminase SGOT/SGPT, ALT/AST	WNL	≤ 2.5 x ULN	2.6 to 5.0 x ULN	5.1 to 20.0 x ULN	> 20.0 x ULN
Alkaline phosphatase	WNL	≤ 2.5 x ULN	2.6 to 5.0 x ULN	5.1 to 20.0 x ULN	> 20.0 x ULN
Portal vein flow (Veno-occlusive Disease)	Normal	-	Decreased portal vein flow	Reversal/retrograde portal vein flow	-

PULMONARY					
TOXICITY	**Grade 0**	**Grade I**	**Grade II**	**Grade III**	**Grade IV**
Cough	Absent	Mild, relieved by non-prescription medication	Requiring narcotic antitussive	Severe cough or coughing spasms, poorly controlled or unresponsive to treatment.	-
Pulmonary Function, Dyspnoea	None or no change	Asymptomatic, abnormal PFT's	Dyspnoea on significant exertion	Dyspnoea at normal level of activity	Dyspnoea at rest
PA 0_2 – change from pre-treatment normal value	≥ 90%	≥75 - <90%	≥50 - <75%	≥25 - <50%	<25%
Carbon Monoxide Diffusion Capacity (DL_{CO})	100 - 75%	74 - 65%	64 - 55%	54 - 40%	< 40%
Vital Capacity (VC)	100 - 75%	74 - 65%	64 - 55%	54 - 40%	< 40%

RENAL					
TOXICITY	**Grade 0**	**Grade I**	**Grade II**	**Grade III**	**Grade IV**
Proteinuria	Normal	1 + or < 3 g L	2 - 3 + or 3 - 10 g/L	4 + or > 10 g/L	Nephrotic syndrome
Haematuria	Negative	Microscopic only	Intermittent gross bleeding, no clots	Persistent gross bleeding or clots. May require catheterisation or instrumentation, or transfusion	Open surgery or necrosis or deep bladder ulceration.
Serum Creatinine Note: adjust to age-appropriate levels for paediatric patients	WNL	< 1.5 x N	1.5 - 3.0 x N	3.1 - 6.0 x N	> 6.0 x N
Glomerular filtration rate (GFR) ml/min/1.73m^2 Note: not listed in CTC Criteria	≥ 90	60 - 89	40 - 59	20 - 39	≥ 19
Tubular Toxicity (Overall*) Note: not listed in CTC Criteria	None	Increase of β2 microglobulin and or lysozyme in urine. Mild hyperamino-aciduria (HAA)	Decrease of phosphate reabsorption (TRP 75 - 85%) glucosuria < 10 mol /L. Moderate HAA	Debre de Toni-Franconi Syndrome, Hypophosphataemic rickets, tetany. Hyperchloraemic metabolic acidosis, polyuria, dehydration	Prolonged (≥ 5 years) or definitive substitution required, or progressive renal failure
Distal Tubular Toxicity **Early morning urine osmolality EMUO - (mOsm/kg)** Note: not listed in CTC Criteria	≥ 600 or normal response to DDAVP	500 - 599	400 - 449	No symptom BUT 300 - 399 with no response to DDAVP	Nephrogenic diabetes insipidus or < 300 with no response to DDAVP

* For more details concerning tubular and glomerular toxicity after drugs such as ifosfamide or platinum compounds a separate precise grading of nephrotoxicity should be used as described by SKINNER *et al.* (J Clin Oncol. 1993 Jan;11(1):173-90)

BLOOD ELECTROLYTES					
TOXICITY	**Grade 0**	**Grade I**	**Grade II**	**Grade III**	**Grade IV**
Hypernatremia (High Sodium, Na+) mmol/L	WNL	>ULN - 150	>150 - 155	>155 - 160	> 160
Hyponatremia (Low Sodium, Na^+) mmol/L	WNL	<LLN - 130	-	120- <130	< 120
Hyperkalemia (High Potassium, K^+) mmol/L	WNL	>ULN - 5.5	>5.5 – 6.0	>6.0 – 7.0	> 7.0
Hypokalemia (Low Potassium, K^+) mmol/L	WNL	<LLN – 3.0	-	2.5 - <3.0	< 2.5
Hypercalcemia (High Calcium, Ca^{++})	WNL	>ULN – 11.5 mg/dL >ULN – 2.9 mmol /L	>11.5 – 12.5 mg/dL >2.9 – 3.1 mmol/L	>12.5 – 13.5 mg/dL >3.1 – 3.4 mmol L	>13.5 mg/dlL >3.4 mmol/L

TOXICITY	Grade 0	Grade I	Grade II	Grade III	Grade IV
Hypermagnesemia (High Magnesium, Mg^{++})	WNL	>ULN -3.0mg/dL >ULN -1.23mmol/L	-	>3.0-8.0mg/dL >1.23-3.30mmol /L	>8.0mg/dL >3.30mmol /L
Hypomagnesemia (Low Magnesium, Mg^{++})	WNL	<LLN-1.2mg/dL <LLN - 0.5mmol/L	0.9-<1.2mg/dL 0.4-<0.5mmol/L	0.7-<0.9mg/dL 0.3-<0.4mmol/L	<0.7mg/dL <0.3mmol/L

NEUROLOGICAL					
TOXICITY	**Grade 0**	**Grade I**	**Grade II**	**Grade III**	**Grade IV**
Cortical	None	Mild somnolence or agitation, not interfering with function	Moderate somnolence or agitation interfering with function, but not with activities of daily living	Severe somnolence, agitation, confusion, disorientation or hallucinations	Coma, seizures, toxic psychosis
Ataxia (incoordination)	None	Asymptomatic but abnormal on physical exam, not interfering with function	Mild symptoms interfering with function, but not interfering with activities of daily living	Moderate symptoms interfering with activities of daily living	Bedridden or disabling
Confusion	Normal	Confusion or disorientation or attention deficit of brief duration; resolves spontaneously with no sequelae	Confusion or disorientation or attention deficit interfering with function, but not interfering with activities of daily living	Confusion or delirium interfering with activities of daily living	Harmful to others or self; requiring hospitalization
Irritability (children <3 years of age)	Normal	Mild; easily consolable	Moderate; requiring increased attention	Severe; inconsolable	-
Leukoencephalopathy associated radiological findings	None	Mild increase in SAS (subarachnoid space) and/or mild ventriculomegaly; and/or small (+/- multiple) focal T2 hyperintensities, involving periventricular white matter or <1/3 of susceptible areas of cerebrum	Moderate increase in SAS; and/or moderate ventriculomegaly; and/or focal T2 hyperintensities extending into centrum ovale; or involving 1/3 to 2/3 of susceptible areas of cerebrum	Severe increase in SAS; severe ventriculomegaly; near total white matter T2 hyperintensities or diffuse low attenuation (CT); focal white matter necrosis (cystic)	Severe increase in SAS; severe ventriculomegaly; diffuse low attenuation with calcification (CT); diffuse white matter necrosis (MRI)
Seizure(s)	None	-	Seizure(s) self-limited and consciousness is preserved	Seizure(s) in which consciousness is altered	Seizures of any type which are prolonged, repetitive, or difficult to control (e.g., status epilepticus, intractable epilepsy)
Mood	No change	Mild anxiety or depression	Moderate anxiety or depression interfering with function, but not interfering with activities of daily living	Severe anxiety or depression interfering with activities of daily living	Suicidal ideation or danger to self.
Sensory	None or No change	Mild paresthesia or loss of deep tendon reflexes – not interfering with function.	Objective sensory loss or paresthesia interfering with function, but not interfering with activities of daily living	Sensory loss or paresthesia interfering with activities of daily living	Permanent sensory loss that interferes with function
Motor	None or No change	Subjective weakness; no objective findings	Mild objective weakness without significant impairment	Objective weakness with impairment of function	Paralysis

Headache	None	Mild	Moderate or severe but transient	Unrelenting and severe	-
TOXICITY	**Grade 0**	**Grade I**	**Grade II**	**Grade III**	**Grade IV**
Ileus (or neuroconstipation)	None	-	Intermittent, not requiring intervention	Requiring non-surgical intervention	Requiring surgery
Vision	None or No change	-	-	Symptomatic subtotal loss of vision	Blindness

PAIN					
TOXICITY	**Grade 0**	**Grade I**	**Grade II**	**Grade III**	**Grade IV**
Treatment Related Pain	None	Mild	Moderate	Severe	Resistant to treatment
Headache	None	Mild	Moderate or severe but transient	Unrelenting and severe	-

Ototoxicity

For the PNET 4 Study, Ototoxicity will be graded according to the HIT Group criteria (see section 10.4.4.) except for ototoxicity noted on an audiogram at the end of treatment that will be graded according to both the HIT Group and the CTC/Brock criteria.

Appendix M

Practical aspects of Neurological and Endocrine follow-up and Timetable for assessments

1. Introduction

The strongest design for testing of outcome measures is prospective and longitudinal and therefore this will be undertaken in PNET 4 (see table in 1.5). Data collection will thus require several years of commitment by doctors, clinic nurses and data managers as well as parents and patients to provide the necessary information. Ultimately this data will not only inform treatment effects on patient groups, but also aid in identifying patient needs and evaluating effectiveness of interventions.

All the questionnaires have been compiled into colour-coded age appropriate booklets for ease of use. There are six in total, two of which are *self-complete* booklets i.e. a green one to be completed by patients aged between 11 and 16, and a pale yellow one to be completed by patients aged 17 and over (including the assessment at age 20). The *parent-complete* booklets are as follows: pink for parents of children aged between 4 and 7, dark yellow for those of 8 to 10 year olds, blue for those of 11 to 16 year olds, and grey for those of young people aged 17 and 18.

For the cross-sectional data collection although the contents of the questionnaire booklets remain the same, apart from a few minor amendments (see below), the age ranges have been altered. There are four booklets in total, two of which are *self-complete* booklets as before i.e. a green one to be completed by patients aged between 11 and 17 (instead of 16), and a pale yellow one to be completed by patients aged 18 and over (instead of 17). The *parent-complete* booklets are as follows: dark yellow for those of 8 to 10 year olds (the same as before), blue for those of 11 to 17 year olds (instead of 11-16 and 17&18). The pink booklet is redundant at this stage in the UK as all the children are at least 10 years old.

2. Organisation of data collection in PNET 4

Collection of this information will be coordinated by a lead person in each national group and may vary according to national practice. In general it is likely that, in most national groups, oncology clinic nurses or data co-ordinators will be given responsibility for distributing and collecting the questionnaire booklets. Ascertainment of the information whose collection is proposed will therefore require the time of a small SIOP group of national lead persons.

The lead person in each national group will define the mechanisms within that group for distributing appropriate forms and reminders to centres with patients enrolled in PNET 4. Each participating centre will identify a named individual responsible for returning completed questionnaires. Paediatric oncologists, clinic nurses or data managers (according to local preference and practice) will take responsibility for approaching patients and parents to complete the questionnaire booklets. Parents and patients aged 11 or more, will be asked to complete the relevant questionnaire booklets when attending clinics for routine follow-up, where possible, or alternatively they will be mailed the appropriate questionnaire booklets to complete at home and return to the named individual at the local children's cancer centre in a stamped addressed envelope.

3. Description of measures

A. Questionnaires: this study proposes a minimum core dataset of information about health status and behaviour in children which will be provided by two short questionnaires, the Health Utilities Index (HUI) and the Strengths and Difficulties Questionnaire (SDQ), completed by parents post surgery/before radiotherapy, at the end of chemotherapy and at three and five years after diagnosis In addition, at the age of 20, the patient will be asked to complete the HUI questionnaire, and in the UK only, the Australian SDQ which is more appropriate than the UK version for this age group. These are both short but wide-ranging generic (as opposed to disease-specific) questionnaires completed by parents that have previously been shown to discriminate well between children with brain tumours and those with tumours of other types and between children with different degrees of disability associated with treated brain tumours. In children aged 11 or more, the children themselves will also be asked to complete versions of the two questionnaires intended for self-completion. In addition a measure of the quality of life, as perceived by both parent and patient is desirable and will be available as an optional additional set of data, the precise choice of questionnaire available to national groups varying according to language.

(i) The Health Utilities Index (HUI)

The Health Utilities Index is a 15-item questionnaire with 1 additional global question that has been shown to be acceptable, reliable and valid in many childhood populations[89 106] and to be sensitive to clinical problems (excepting behavioural problems) in populations of children who have been treated for brain tumours[90]. The HUI is a wide ranging measure of health status which, since it has the properties of an interval scale, allows comparison of global Health Status or of the 'attributes' of vision, hearing, speech, dexterity, ambulation, cognition, emotion, and pain, each of which can be assigned to a health state which can then be converted to a utility value of one (unaffected) or at a lower value (on a scale on which death has a score of zero) depending on the degree of functional disturbance. The information can be used flexibly for groups of children to compare the number of affected attributes, or to compare the number of children falling below a "cut-off" level on a given attribute (such as cognition), or to compare the overall scores. Particularly relevant HUI data are available for 42 French children with medulloblastoma, the majority treated on SFOP protocols[91]. The HUI has been thoroughly tested in several European languages, including English, German, French, Spanish, Dutch, Italian and Portuguese.

(ii) The Strengths and Difficulties Questionnaire (SDQ)

The Strengths and Difficulties Questionnaire[107 108 109] is a 25-item questionnaire with subscales for hyperactivity, emotional symptoms, conduct problems, peer relationships, and prosocial behaviour. It was developed from the longer Rutter scales that have been extensively used for this purpose since the 1960s. Supplementary questions on the impact of the symptoms on the family are available. Versions are available for parents to complete on 3 to 4 year olds, 4 to 16 year olds and for patients over 11 to complete on themselves and for teachers to complete on school age children but we have not included teacher's responses, which are more difficult to ascertain, in the minimum core dataset.

The SDQ is sensitive and specific in the detection of psychiatric problems in children, as diagnosed by

semi-structured psychiatric interview[108], including those whose problems are secondary to known brain injury[107]. The SDQ discriminates between children who do and do not display behaviours suggestive of underlying disorders of attention, emotionality, conduct or peer relationships and, as such, the HUI and the SDQ are complementary with little overlap[90]. It also confirms the clinical experience of a very high prevalence of such problems in children treated for brain tumours. The text of questionnaires, scoring system, publication abstracts and other information are available at the SDQ website: http://www.iop.kcl.ac.uk/IoP/Departments/ChildPsy//sdq/b7.stm. Translations from English potentially relevant to a European study include Catalan, Chinese, Croatian, Czech, Dutch, French, Finnish, German, Gaelic, Greek, Gujarati, Hindi, Hungarian, Irish, Italian, Norwegian, Polish, Portuguese, Punjabi, Romanian, Russian, Serbian, Slovenian, Spanish, Swedish, Tamil, Turkish, Ukrainian, Urdu and Welsh.

(iii) Quality of life studies (optional according to decisions of national groups)

It would be desirable to supplement these measures with some measures of the child's own experience of illness and perception of quality-of-life. There is, as yet, no such measure that has been shown ready to be applied across Europe, but there are three measures of which at least one may be used in most countries:

1. The Paediatric Quality of Life Inventory (PedsQL)[103], suitable for use in many languages.
2. The PEDQOL, developed under the auspices of the EORTC and SIOP. This is available in German, English, French Dutch, Swedish, Finnish, Italian, Spanish and Russian. It has been validated so far in its German version[110 111], in Spain and Italy on norm groups as well as on brain tumour patients. It is also currently in use for prospective evaluation in the German HIT studies as well as in brain tumour patients in Italy.
3. The CHQ-PF 28 (Child Health Questionnaire, parent form)[112] is already in use in the German HIT studies and will also be used in the UK. The 28 question version of this questionnaire is not yet available in other languages.

(iv) Quality of life studies (mandatory for 20 year olds)

Patients aged 17 years and over will be asked to complete the QLQ-C30, a questionnaire measure of the patient's own perception of quality of life developed by the EORTC for use in adults with cancer (EORTC manual, 1993, Brussels) including a module specifically for adults with brain tumours.

(vi) Cross-sectional data collection

The CHQ-PF28 will be removed. The BRIEF (Behavior Rating Inventory of Excutive Funtion) questionnaire will be included. A parent report version will be completed by parents of children aged 5-17. The self-report version of the BRIEF will be included in the booklet for patients aged 18 and over. The MEES which was in the original booklets for the longitudinal collection of PNET 4 quality of survival data, remains. This questionnaire includes questions relating to the child's education, treatment, social and employment status (if old enough). There is a parent report form for children aged 11 years and older, and a self-report equivalent for 18 year olds and older. For children younger than 11, some of the questions which are not relevant to this age group have been removed.

B. Audiology – **see section 10.4.4** (main text)

C. Endocrinology

Growth and endocrine data

a) At diagnosis record :
Reported birthweight (kg)
Reported gestational age at birth (weeks/40)
Measure parental heights (cm)

b) At each data point (see table, Section 1.5)

i) Date (for calculation of decimal age)

ii) Auxology
"Stretched " Standing Height (cm), "stretched sitting height (cm), Weight (kg), Pubertal ratings (as per Marshall & Tanner 1969[87] & 1970[88]) (see key on data form).

Patients should have this auxology and pubertal assessment performed at least annually (from which pubertal onset can then be assessed to at least the nearest year).
These data will be reported to the data centre on an annual basis.

iii) Serum Biochemistry
Gonadotropins, LH (iu/L), FSH (iu/L), and Estradiol (pmol/L) (if female) or testosterone (nmol/L) (if male), Free thyroxine, T4 (nmol/L), thyrotropin, TSH (mU/L).

This biochemical assessment should be undertaken at five time points:
Following surgery/before radiotherapy, at the end of chemotherapy, 3 and 5 years post diagnosis and at aged 20 years.

Measurement of gonadotrophins and sex steroids is restricted those children aged eight years or more at the time of the assessment.

Blood for LH/FSH should be timed to correspond to the follicular phase of the menstrual cycle i.e. at between Day 2 and 6 of the cycle in those women who are *spontaneously* menstruating (i.e. not on sex hormone replacement).

Measurement of free thyroxine, T4 (nmol/L) and thyrotropin, TSH (mU/L) should be undertaken in children of all ages.

iv) Hormone replacement therapy (with starting and finishing dates) or contraceptive medication.

c) Also Note and record (reported annually):
Age at onset of puberty (breast budding: female, 4ml testicular volumes: males)
Spontaneous or induced (exogenous sex steroids) puberty

Age at menarche and last menstrual period (LMP)
Regularity/irregularity of spontaneous menstrual cycle

Guidelines for Endocrine Investigation

1. Date (vital for decimal age calculation)

2.Height
Heights should be measured by the same one or two trained nurses using the "stretched technique", where a line drawn from the outer canthus of the eye to the tip of the ear lobe is parallel to the floor. The Harpenden stadiometer is the most accurate and robust equipment, but must be regularly calibrated and carefully maintained (preferably locked when out of use).

3.Sitting height
A Harpenden sitting height table, or the same, hard stool of fixed height used against the Harpenden stadiometer is necessary. The child sits with hips and knees flexed 90º and a straight back.

4.Pubertal development (Tanner staging)
This should be performed annually according to Tanner[87 88].
Testicular volume should be estimated by Prader Orchidometry. Testicular volume 4ml in males, or breast buds in females indicate onset of puberty which should be recorded.

5. Biochemistry

- Vital for detection and treatment of subclinical glandular toxicity and prevention of later complications of hormone deficiency.

- Interpretation relies heavily on accurate clinical information, pubertal staging and knowledge of age- and sex- standardised reference norms (see below).

- Is likely to form part of annual or 2-yearly surveillance strategy in many centres thus resulting in possible hormone substitution at interim times not requested on central data collection. It is imperative the pre-treatment levels are documented for comparison of "toxicity" data in randomised arms of this study.

Biochemistry of puberty
The hypothalmo-pituitary-gonadal axis is suppressed to undetectable levels at about 6 post-natal months. Re-activation pre-dates and heralds clinical puberty. As puberty progresses, the amplitude and frequency of secretion increases until 24h pulsatility is achieved. The latter is necessary for reproductive potential and the female LH ovulatory surge.

Raised FSH levels for age are an inverse surrogate marker of reduced germ cell capacity in both sexes. However, these serum values must be interpreted with respect to age- sex- and cycle-timed norms as well as any contraceptive or sex steroid replacement therapy. For instance, raised LH levels are an inverse surrogate marker of reduced sex steroid production and their suppression indicates adequacy of

hormone replacement in this situation.

Thus pre- peri- and post-pubertal gonadotropin levels can provide valuable information towards subclinical gonadotoxicity. Endocrine biochemistry may be performed because of clinical concern on annual assessments above as well as protocol requirement (post radiotherapy, end of treatment,3,5 years and at aged 20y). If endocrine therapy is then instigated, it is vital the pre-treatment clinical and endocrine data are recorded for interpretation of severity and "time to occurrence".

Endocrine Expertise

Because of the high prevalence of growth failure and/or GH insufficiency at 2 years, and the need to standardize detection and treatment of any hormonal dysfunction, we recommend referral to a paediatric endocrinologist or paediatrician with endocrine expertise by 2 years after diagnosis, or in the presence of any of the biochemical or auxological criteria below.

A. Biochemical criteria for endocrine referral:

- Elevated TSH, and/or low fT4.
  (Thyroxine treatment [at about 100ug/m2] to maintain TSH in normal range and avoid its carcinogenicity in the irradiated thyroid gland).
  If treatment is commenced, please record pre-treatment biochemistry.
- Elevated LH and FSH pre- or post-pubertally as above as above, +/- low pubertal estradiol or testosterone according to reference for age and sex
- Confirming growth hormone disturbance (likely at 2-5 years) should be done in an endocrine department familiar with the hazards and interpretation of these tests.

B. Auxological criteria for mandatory endocrine referral and investigation:

- Less than 4cm annual increment in height at any age.
- Less than 8 cm annual increment in puberty spurt (testes 10-12ml or breast buds)
- Sustained growth at the expense of weight gain and/or early puberty
- Early Puberty onset (breast buds < 9y, female; 4ml testes <10y male)
- Delayed Pubertal onset (>12 y in female, > 13 y in male)
- Pubertal Arrest (no pubertal progress, according to Tanner, in one year).
- Secondary amenorrhoea of > 3 months, or primary amenorrhoea after 13.5 y.

Appendix N

Ethical Considerations

The trial protocol must be approved by the appropriate ethical committee in each country prior to patient entry. The patient's and/or parent's written consent to participate in the study must be obtained after a full explanation has been given concerning the treatment. As well as consent for the clinical trial, consent is required for participation in the biological studies and, depending on national law, consent is needed for data collection, storage, transfer and analysis. Additionally the child should receive an explanation as to his/her means of understanding and should give consent as well if he or she is able to do it.

The right of a patient to refuse to participate without giving reasons must be respected. The patient must remain free to withdraw at any time from protocol without prejudicing his/her further treatment. The study observes the rules for clinical research set out in the ICH/GCP and EC rules of good clinical practice.

Declaration of Helsinki

WORLD MEDICAL ASSOCIATION DECLARATION OF HELSINKI
Ethical Principles for Medical Research Involving Human Subjects

Adopted by the 18th WMA General Assembly
Helsinki, Finland, June 1964
and amended by the
29th WMA General Assembly, Tokyo, Japan, October 1975
35th WMA General Assembly, Venice, Italy, October 1983
41st WMA General Assembly, Hong Kong, September 1989
48th WMA General Assembly, Somerset West, Republic of South Africa, October 1996
and the 52nd WMA General Assembly, Edinburgh, Scotland, October 2000

A. INTRODUCTION

1. The World Medical Association has developed the Declaration of Helsinki as a statement of ethical principles to provide guidance to physicians and other participants in medical research involving human subjects. Medical research involving human subjects includes research on identifiable human material or identifiable data.
2. It is the duty of the physician to promote and safeguard the health of the people. The physician's knowledge and conscience are dedicated to the fulfilment of this duty.
3. The Declaration of Geneva of the World Medical Association binds the physician with the words, "The health of my patient will be my first consideration," and the International Code of Medical Ethics declares that, "A physician shall act only in the patient's interest when providing medical care which might have the effect of weakening the physical and mental condition of the patient."
4. Medical progress is based on research which ultimately must rest in part on experimentation involving human subjects.
5. In medical research on human subjects, considerations related to the well-being of the human subject should take precedence over the interests of science and society.
6. The primary purpose of medical research involving human subjects is to improve prophylactic, diagnostic and therapeutic procedures and the understanding of the aetiology and pathogenesis of disease. Even the best-proven prophylactic, diagnostic, and therapeutic methods must continuously be challenged through research for their effectiveness, efficiency, accessibility and quality.
7. In current medical practice and in medical research, most prophylactic, diagnostic and therapeutic procedures involve risks and burdens.
8. Medical research is subject to ethical standards that promote respect for all human beings and protect their health and rights. Some research populations are vulnerable and need special protection. The particular needs of the economically and medically disadvantaged must be recognized. Special attention is also required for those who cannot give or refuse consent for themselves, for those who may be subject to giving consent under duress, for those who will not benefit personally from the research and for those for whom the research is combined with care.
9. Research Investigators should be aware of the ethical, legal and regulatory requirements for research on human subjects in their own countries as well as applicable international requirements. No national ethical, legal or regulatory requirement should be allowed to reduce or eliminate any of the protections for human subjects set forth in this Declaration.

B. BASIC PRINCIPLES FOR ALL MEDICAL RESEARCH

10. It is the duty of the physician in medical research to protect the life, health, privacy, and dignity of the human subject.

11. Medical research involving human subjects must conform to generally accepted scientific principles, be based on a thorough knowledge of the scientific literature, other relevant sources of information, and on adequate laboratory and, where appropriate, animal experimentation.

12. Appropriate caution must be exercised in the conduct of research which may affect the environment, and the welfare of animals used for research must be respected.

13. The design and performance of each experimental procedure involving human subjects should be clearly formulated in an experimental protocol. This protocol should be submitted for consideration, comment, guidance, and where appropriate, approval to a specially appointed ethical review committee, which must be independent of the investigator, the sponsor or any other kind of undue influence. This independent committee should be in conformity with the laws and regulations of the country in which the research experiment is performed. The committee has the right to monitor ongoing trials. The researcher has the obligation to provide monitoring information to the committee, especially any serious adverse events. The researcher should also submit to the committee, for review, information regarding funding, sponsors, institutional affiliations, other potential conflicts of interest and incentives for subjects.

14. The research protocol should always contain a statement of the ethical considerations involved and should indicate that there is compliance with the principles enunciated in this Declaration.

15. Medical research involving human subjects should be conducted only by scientifically qualified persons and under the supervision of a clinically competent medical person. The responsibility for the human subject must always rest with a medically qualified person and never rest on the subject of the research, even though the subject has given consent.

16. Every medical research project involving human subjects should be preceded by careful assessment of predictable risks and burdens in comparison with foreseeable benefits to the subject or to others. This does not preclude the participation of healthy volunteers in medical research. The design of all studies should be publicly available.

17. Physicians should abstain from engaging in research projects involving human subjects unless they are confident that the risks involved have been adequately assessed and can be satisfactorily managed. Physicians should cease any investigation if the risks are found to outweigh the potential benefits or if there is conclusive proof of positive and beneficial results.

18. Medical research involving human subjects should only be conducted if the importance of the objective outweighs the inherent risks and burdens to the subject. This is especially important when the human subjects are healthy volunteers.

19. Medical research is only justified if there is a reasonable likelihood that the populations in which the research is carried out stand to benefit from the results of the research.

20. The subjects must be volunteers and informed participants in the research project.

21. The right of research subjects to safeguard their integrity must always be respected. Every precaution should be taken to respect the privacy of the subject, the confidentiality of the patient's information and to minimize the impact of the study on the subject's physical and mental integrity and on the personality of the subject.

22. In any research on human beings, each potential subject must be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail. The subject should be informed of the right to abstain from participation in the study or to withdraw consent to participate at any time without reprisal. After ensuring that the subject has understood the

information, the physician should then obtain the subject's freely-given informed consent, preferably in writing. If the consent cannot be obtained in writing, the non-written consent must be formally documented and witnessed.
23. When obtaining informed consent for the research project the physician should be particularly cautious if the subject is in a dependent relationship with the physician or may consent under duress. In that case the informed consent should be obtained by a well-informed physician who is not engaged in the investigation and who is completely independent of this relationship.
24. For a research subject who is legally incompetent, physically or mentally incapable of giving consent or is a legally incompetent minor, the investigator must obtain informed consent from the legally authorized representative in accordance with applicable law. These groups should not be included in research unless the research is necessary to promote the health of the population represented and this research cannot instead be performed on legally competent persons.
25. When a subject deemed legally incompetent, such as a minor child, is able to give assent to decisions about participation in research, the investigator must obtain that assent in addition to the consent of the legally authorized representative.
26. Research on individuals from whom it is not possible to obtain consent, including proxy or advance consent, should be done only if the physical/mental condition that prevents obtaining informed consent is a necessary characteristic of the research population. The specific reasons for involving research subjects with a condition that renders them unable to give informed consent should be stated in the experimental protocol for consideration and approval of the review committee. The protocol should state that consent to remain in the research should be obtained as soon as possible from the individual or a legally authorized surrogate.
27. Both authors and publishers have ethical obligations. In publication of the results of research, the investigators are obliged to preserve the accuracy of the results. Negative as well as positive results should be published or otherwise publicly available. Sources of funding, institutional affiliations and any possible conflicts of interest should be declared in the publication. Reports of experimentation not in accordance with the principles laid down in this Declaration should not be accepted for publication.

C. ADDITIONAL PRINCIPLES FOR MEDICAL RESEARCH COMBINED WITH MEDICAL CARE

28. The physician may combine medical research with medical care, only to the extent that the research is justified by its potential prophylactic, diagnostic or therapeutic value. When medical research is combined with medical care, additional standards apply to protect the patients who are research subjects.
29. The benefits, risks, burdens and effectiveness of a new method should be tested against those of the best current prophylactic, diagnostic, and therapeutic methods. This does not exclude the use of placebo, or no treatment, in studies where no proven prophylactic, diagnostic or therapeutic method exists.
30. At the conclusion of the study, every patient entered into the study should be assured of access to the best proven prophylactic, diagnostic and therapeutic methods identified by the study.
31. The physician should fully inform the patient which aspects of the care are related to the research. The refusal of a patient to participate in a study must never interfere with the patient physician relationship.
32. In the treatment of a patient, where proven prophylactic, diagnostic and therapeutic methods do not exist or have been ineffective, the physician, with informed consent from the patient, must be free to use unproven or new prophylactic, diagnostic and therapeutic measures, if in the physician’s judgement it offers hope of saving life, re-establishing health or alleviating suffering. Where possible, these

measures should be made the object of research, designed to evaluate their safety and efficacy. In all cases, new information should be recorded and, where appropriate, published. The other relevant guidelines of this Declaration should be followed.

Appendix Q Schedule of data form return

This schedule is for data forms only. See table in section 1.5 for schedule of completion and return of parent-complete and self-complete questionnaire booklets.

Timing	Form Number	Form Name	Form Return	Date Form Sent
Diagnosis	**Form 1** 2 pages	**Registration and Randomisation**	Before Day 28 (ensure pathology sent for central review)	
	Form 2A **Form 2B**	**To Radiology review** **Radiology review**	On-line or within one year (Before start or within one week of start of radiotherapy for National Groups undertaking on-line Quality Control -or within one year)	
	Form 3	**Neurosurgery**	Within 3 months	
	Form 4	**Pathology review & Biological studies**	Within 3 months (ensure pathology sent for central review)	
Before RT	**Form 5** 3 pages	**Status after surgery and before Radiotherapy**	Within 3 months	
	Form 6A **Form 6B** 2 pages	**To RT quality control** **RT quality control**	On-line or within one year (Before start or within one week of start of radiotherapy for National Groups undertaking on-line Quality Control- or within one year)	
During treatment	**Form 7** 9 pages	**Radiotherapy**	Within 3 months of the end of radiotherapy	
	Form 8	**Chemotherapy toxicity**	After every second course of chemotherapy (complete form after every course)	
Post treatment	**Form 9**	**Post treatment growth &l puberty**	End of chemotherapy thereafter Annually	
	Form 10 2 pages	**Post treatment hormone levels & hormone treatment**	End of chemotherapy 3 years 5 years Age 20 years	
	Form 11 3 pages	**Post treatment neurology & education**	End of chemotherapy 3 years 5 years Age 20 years	
	Form 12	**Follow up relapse and death**	End of chemotherapy thereafter Annually or within one month after relapse or death (within 24 hours if death due to SAE)	
	Form 13	**Posterior fossa relapse**	If relapse involves posterior fossa inform National RT Quality Control Coordinator	
Any time	**Form 14**	**Serious adverse events**	Within 24 hours of the knowledge of the event	