COOPERATIVE MULTICENTRE STUDY FOR CHILDREN AND ADOLESCENTS WITH LOW GRADE GLIOMA

SIOP-LGG 2004

UK SUPPLEMENT (RG_09-201)

Version 4.0_a, 14 September 2010

TO BE USED IN CONJUNCTION WITH THE SIOP-LGG PROTOCOL

REFER TO THE FULL SIOP – LGG PROTOCOL FOR DETAILS

UK Chief Investigator: Dr Sue Picton

MREC number: MREC/03/4/108	MREC Approval Date: 10th August 2004
Eudract number: 2005-005377-29	MREC Amendment Date: 13th March 2006
Protocol Version: 3.0 August 2007	MREC Amendment 2 Date: 11th August 2008
UK Start Date: 1st September 2004	

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Amendment: RG_09-201 (formally known as CNS 2004 03) A3 – 14 September 2010

List of A3 amendments

Page	Section	Amendment
Throughout	NA	Footer: Version 3- 18 April 2008 changed to Version 4.0- 14 September 2010 Study code RG_09-201 added to footer
Throughout	NA	"CCLG" changed to CRCTU
Cover	NA	CCLG logo deleted Study code CNS 2004 03 changed to RG_09-201 Version 3- 18 April 2008 changed to Version 4.0, 14 September 2010 CCLG contact details changed to CRCTU contact details
2	NA	List of A3 amendments added
55	23.2	Wording changed from '...knowledge of the event to the CCLG Data Centre as per CCLG Standard Operating Procedure using the CCLG Serious Adverse Event Report Form..' to '...knowledge of the event to the CRCTU using a separate SAE form..'
		Non Substantial Amendment
7	Key contacts	UK Chief Investigator Sue Picton contact details updated to reflect change of address
Throughout	NA	Updated page numbers and footers
Patient Information Sheets	NA	Hypothalamic chiasmatic visual pathway tumours: observation study: Amended footer on Consent form for patients 16+ years
Patient Information Sheets	NA	Observational study- Non-hypothalamic chiasmatic visual pathway tumours: Amended footer on Information Sheets for GP

Amendment: CNS 2004 03 A2 – 18 April 2008

List of A2 amendments

Page	Section	Amendment
Throughout	NA	Footer: Version 2 February 2006 changed to Version 3- 18 April 2008
Throughout	NA	"UKCCSG" changed to "CCLG"
Cover	NA	Version 2 February 2006 changed to Version 3- 18 April 2008
		Confidentiality statement added
		Deletion of text "Please destroy any previous versions"
2-4	NA	List of amendments updated
6	Key contacts	Contact details for Jennie Lucas and Suzanne Stevens deleted
		Addition of contact details for UK Trial Coordinator
		Text changed from "Other contacts" to "UK Investigators"
7-9	Index	Index updated
10-12	Synopsis	Synopsis added

13	1	Text changed from "adolescents" to "young people"
14	4	Text changed from "adolescents" to "young people"
		Upper age limit changed from "16 years" to "25 years (25th birthday)"
		Addition of definitions of eligibility for patients aged 16+
		Addition of text "and regulatory"
	5	Text changed from "All patients with NF1 receiving chemotherapy as their first non-surgical treatment are not eligible…" to "All patients up to the age of 16 years (16th birthday) without NF1 receiving chemotherapy as their first non-surgical treatment are eligible…"
27	15.2.4	Text changed from "adolescents" to "young people"
34	17.2	Addition of text "following toxicity"
		Addition of text regarding flowcharts in Appendix 1
	17.2.1	Addition of text "Patients over 12 months of age who are under nourished (particularly if suffering from Diencephalic syndrome) and who weigh <10kg can be given 75% doses with the aim to increase to 100% once the nutritional state improves"
37	17.2.4	Text changed from "The two combinations shall be given a maximum of 5 times each to limit cumulative doses." to "The two combinations shall be given a maximum of 5 times each (i.e. 10 x 6 week chemotherapy cycles in total) to limit cumulative doses, however treatment must not continue beyond week 81 from the start of chemotherapy. NB: stop at week 81 or after 10 x 6 week cycles of alternative chemotherapy, whichever comes first."
54	23.2	Clarification of SAE reporting procedures
		Addition of definition of SAEs
		Clarification of events that should not be reported as SAEs
55	23.2.1	Definition of SARs and SUSARs and clarification of handling procedures
56	Appendix 1	Addition of chemotherapy flowcharts
67	Appendix 2	Updated Index of PIS and consent forms

List of A2 Amendments to PIS and Consent Forms

Section	Page	Amendment
Throughout	NA	Version number and dates updated
		Deleted footer "Documents approved with LGG2 UK Supplement Version 2- February 2006"
		Pagination of footers
		Study title changed from "Study for Children and Adolescents with Low Grade Glioma" to "Cooperative Multicentre Study for Children and Adolescents with Low Grade Glioma (CNS 2004 03)"
		"UKCCSG" changed to "CCLG"
All parent/guardian information (except randomised study and		Deletion of text "This will also include information about any scans performed"

radiotherapy)		
All parent/guardian information		Addition of information regarding central pathology and radiology reviews.
		Old confidentiality text deleted and new information added.
All information for patients aged 13-15 years		Addition of information regarding central pathology and radiology reviews
		Old confidentiality text deleted and new information added
All parent/child consent forms		Deletion of "Centre number" and "MREC reference number"
		Addition of "Centre"
		"Researcher" changed to "Principal Investigator"
		Point 3: "Company name" deleted
		Point 3 clarified with updated wording
		Addition of point 6 regarding informing GP of study participation
		Text changed from "1 for researcher" to "1 for site file"
All Consent forms for patients aged 16+ years		Consent forms for patients aged 16+ years added to each section (except randomised study)
All GP information		Numbering of questions removed
		Text changed from "Whilst in our care the parent/guardian of your patient has given permission for their child to take part…" to "Your patient…… (DOB…….) will be taking part…"
		Text changed from "children" to "patients"
		Text changed from "The relevant members of the family…" to "Your patient/relevant members of the family…"
		Addition of text "their permission/"
Hypothalamic chiasmatic visual pathway tumours: observation study		
Information for parents/guardians and patients aged 13+ years	1	Title changed from "Information sheets for Parents and Teenage Patients" to "Information Sheet for Parents/Guardians and Patients Aged 13+ Years"
Study of treatment of low grade gliomas in children with neubrofibromatosis type-1		
Information for parents/guardians and patients aged 13+ years	1	Title changed from "Information sheets for Parents and Teenage Patients" to "Information Sheet for Parents/Guardians and Patients Aged 13+ Years"
Information for younger children	1	Text changed from "patients" to "children"
	2	Text changed from "Thank you for reading this information sheet" to a picture of a dog with the caption "Thank you"
A randomised comparison of two drugs versus three drugs in induction chemotherapy		
Parent/Guardian Information	1	Title changed from "Parent Information Sheet" to "Parent/Guardian Information Sheet"
Information for 13-15 year olds	1	Title changed from "Information sheet for 14-16 year olds" to "Information sheet for 13-15 year olds"
Information for 8-12 year olds	1	Title changed from "Information sheet for 8-14 year olds" to "Information sheet for 8-12 year olds"

	2	Question 5: text changed from “place” to “city”
		Question 9: text changed from “if” to “of”
	3	Question 12: text changed from “tumour” to “lump”
A Study of Conformal Radiotherapy for Low Grade Glioma		
Parent/Guardian Information	1	Title changed from “Parent Information Sheet” to “Parent/Guardian Information Sheet”
		Deletion of Chief and Local Investigator details
		Question 2: addition of text “patients older than 16”
		Question 2: text changed from “children older than 14, aged 8-14…” to “children aged 13-15, aged 8-12…”
Information for young persons aged 16+ years	1	Addition of Information sheet for patients aged 16+ years
Information for children aged 13-15	1	Title changed from “Information sheet for children aged 14 and over” to “Information for children aged 13-15”
		Deletion of Chief and Local Investigator details
Information for children aged 8-12	1	Title changed from “Information sheet for children aged 8-14” to “Information for children aged 8-12”
		Deletion of Chief and Local Investigator details
	2	Question 7: Text changed from “Thank you for reading this sheet” to a picture of a dog with the caption “Thank you”
		Deletion of contact details for Roger Taylor
		Addition of text “[local investigator, phone number]”
Information for children aged less than 8	1	Deletion of Chief and Local Investigator details
Information for General Practitioners	1	Addition of Information sheet for General Practitioners
For those receiving non-randomised chemotherapy treatment		
Information for parents/guardians and patients aged 13+ years	1	Title changed from “Information sheets for Parents and Teenage Patients” to “Information Sheet for Parents/Guardians and Patients Aged 13+ Years”
Information for younger children	1	Text changed from “patients” to “children”
	2	Text changed from “Thank you for reading this information sheet” to a picture of a dog with the caption “Thank you”

Amendment: CNS 2004 03 A1 – February 2006

List of A1 amendments

Page	**Amendment**
Cover	SIOP-LGG 2003 changed to 2004 - in line with the Amendment of the Main protocol Version 1 14/04/2003. Addition of ‘Version 2’ Addition of notice to destroy previous versions Amendment of document ref and version in Footer
Throughout	Amendment of page numbers in references to main protocol *(will need to be rechecked once tracked changes removed)*

3-4	UKCCSG Statistician changed from Claire Weston to Suzanne Stevens Amendment to contact details for Roger Taylor
5-7	Contents page numbering amended
8	1.Introduction SIOP-LGG 2003 changed to 2004
9	4. Eligibility Criteria - Histology Amendment of the ICD O-Code for pilocytic Astrocytoma °I from 9241/3 to 9421/1 and Desmoplastic Infantile Ganglioma °I from 9505/0 to 9412/1
14	13.2 Recommended Investigations – Addition of Neuroendocrine investigations
18	14.4 Central Radiological Review Amendment of text to 'For assessing response to chemotherapy or radiotherapy all relevant scans have to be sent in for review during the pre-treatment and treatment periods'
24, 26	16.1 Neuropathological guidelines Path review update to include reference to the UKCCSG CNS Pathology Review system
29	17.2 Chemotherapy – guidelines Addition of text: 'alternative consolidation in case of allergy or early progression.'
44-46	21.3 Ophthlamology - update to colour vision test and addition of chart for contrast sensitivity + additional instructions
47	21.5 Documentation - amendment to opthalmology documentation instruction
50	Appendix 1 - Amendments to list of Patient Information Sheets
84-90	Inclusion of Patient Information Sheets for 4. Observational Study - Non-Hypothalamic chiasmatic visual pathway tumours – MREC Approved Feb 2005
91-102	Inclusion of Patient Information Sheets for 5. Radiotherapy Treatment Study – MREC Approved Feb 2005
103-109	Addition of New Patient Information Sheets for 6. Non Randomised Chemotherapy Treatment - To be approved

Amendment – 28/01/2005 (MREC Approved 04/02/2005)
Addition of Patient Information Sheets for patients receiving Radiotherapy treatment and Observation Study Patients with non-hypothalamic visual pathway tumours. These documents were not previously included in the UK Supplement dated July 2004 but were issued following MREC approval in February 2005 via the UKCCSG website. They have now been included in the above list as part of Amendment - CNS 2004 03 A1 and incorporated into the LGG2 UK Supplement Version 2 – Feb 2006.

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INDEX

SYNOPSIS

Title

Cooperative multicentre study for children and adolescents with low grade glioma: SIOP-LGG 2004

Trial Aims

- Offer a uniform, standardised concept for the treatment of children and young people affected by low grade glioma
- Improvement of progression free survival
- Investigation of standardized treatment recommendations
- Reduction of the rate and intensity of possible late effects

Primary end-point

- Assessment of progression-free survival

Secondary endpoints

- Overall survival
- Assessment of integral dose to tumor and normal tissue and evaluation on the impact on long-term toxicity
- Assessment of tumor response to radiotherapy by imaging and clinical investigations
- Assessment of progression-free and overall survival, acute and long-term toxicity of cranio-spinal irradiation in metastatic disease

Sample size and duration

- International projected accrual of patients not affected by NF1: 60 chemotherapy; 40 radiotherapy patients/year.
- International projected total accrual of patients not affected by NF1: 360 chemotherapy; 240 radiotherapy patients.
- No projected accrual for treated patients affected by NF1 and patients on observation.
- UK projected total accrual of patients not affected by NF1: 110 chemotherapy patients, equating to approximately 19 patients per year.
- Expected total trial duration: 9.5 years (6 year recruitment, 1.5 years treatment, followed by an observation period of 2 years).

Trial treatment

The Investigational Medicinal Products (IMPs) to be studied in this trial are Etoposide, Vincristine, Carboplatin, Cisplatin and Cyclophosphamide.

Trial design

Phase III clinical trial with three treatment groups:

- Group 1- Children not affected by NF I with low grade glioma of the supratentorial midline
- Group 2- Children not affected by NF I with low grade gliomas of all other sites
- Group 3- Children affected by NF I with low grade glioma of all sites

There are three "strategy" subgroups:

- Observation group

- Treatment group at diagnosis
- Treatment group after observation

Trial treatment consists of the following options:

- **Non-randomised chemotherapy:**
  Standard induction + consolidation (Vincristine & Carboplatin)

- **Randomised chemotherapy**
  Intensified induction (Vincristine, Carboplatin & Etoposide) + consolidation
  Vs Standard induction (Vincristine & Carboplatin) + consolidation

  N.B. In case of allergy or early progression **alternative consolidation** can be given (Vincristine, Cisplatin & Cyclophosphamide)

- **Radiotherapy**

Eligibility Criteria

Inclusion criteria

- Children and young people up to the age of 25 years (25^{th} birthday).
- Glioma of low grade malignancy according to ICD O Code.
- Intracranial and/or spinal cord primary site.
- Localized or disseminated tumour.
- Children are eligible for the trial regardless of the presence of associated genetic disease.
- Written informed consent.
- National and local ethical and regulatory approval.

Exclusion criteria

- Diffuse tumours of the pons, even if histologically an Astrocytoma I^o or II^o is diagnosed.
  Exception: pontine glioma II^o in NFI patients may be entered into the study.
- Patients presenting with rare intracranial neoplasms of low grade malignancy, but of non-glial origin may be treated according to this protocol but will not be included in the randomised trial. Refer to section 6.
- Patients who have had treatment with chemo- or radiotherapy prior to entering the study will be evaluated separately.
- Pre-existing impairment of health status, making the conduct of the study impossible or ethically unwise.
- Pregnancy or lactation period.
- NB: Concomitant medication for associated or other conditions (e.g. steroids, hormone replacement, anticonvulsants) should be recorded, but it is not an exclusion criteria.

Toxicity monitoring

- Whenever a toxicity event occurs, the toxicity rate will be newly calculated as outlined in section 17 page 168 of the SIOP-LGG protocol.
- Serious Adverse Events must be reported immediately on knowledge of the event.

Central neuroradiological, and pathological review

Central review of pathology slides and/or of radiological images will be undertaken. This is compulsory in all children in the randomised chemotherapy arm.

Ophthalmology assessments

Children who have been diagnosed as having optic pathway and hypothalamic glioma, require regular ophthalmological examinations at defined timepoints.

Statistical considerations

Sample size (Patients not affected by NF1)

Chemotherapy: With a significance level of 5 %, 360 patients are necessary to obtain a power of 90% while performing a three step group sequential design according to Pampallona & Tsiatis for the two-sided log-rank-test on difference. The sample size was calculated for an one-step design with nQuery Advisor 3.0 and the sample size was adapted to the 3-step group sequential design.

Radiotherapy: It is expected that 240 patients will be recruited during 6 years. The analysis will be done according to the intention-to-treat principle. Additionally there will be made a per-protocol analysis. All analyses will be performed exploratively.

Early stopping and Interim analysis

Chemotherapy: The trial has to be stopped, if the probability for a toxic event exceeds 25 %. Interim analyses will be performed after 1/3 and 2/3 of expected events have occurred, unless the trial was stopped before. The trial will be terminated after an interim analysis, if the main question can already be answered at this interim analysis or the chance to answer the main question is low while continuing the trial.

Radiotherapy: The trial has to be stopped, if the probability for a toxic event exceeds 30 % or if more than one patient dies because of radiotherapy.

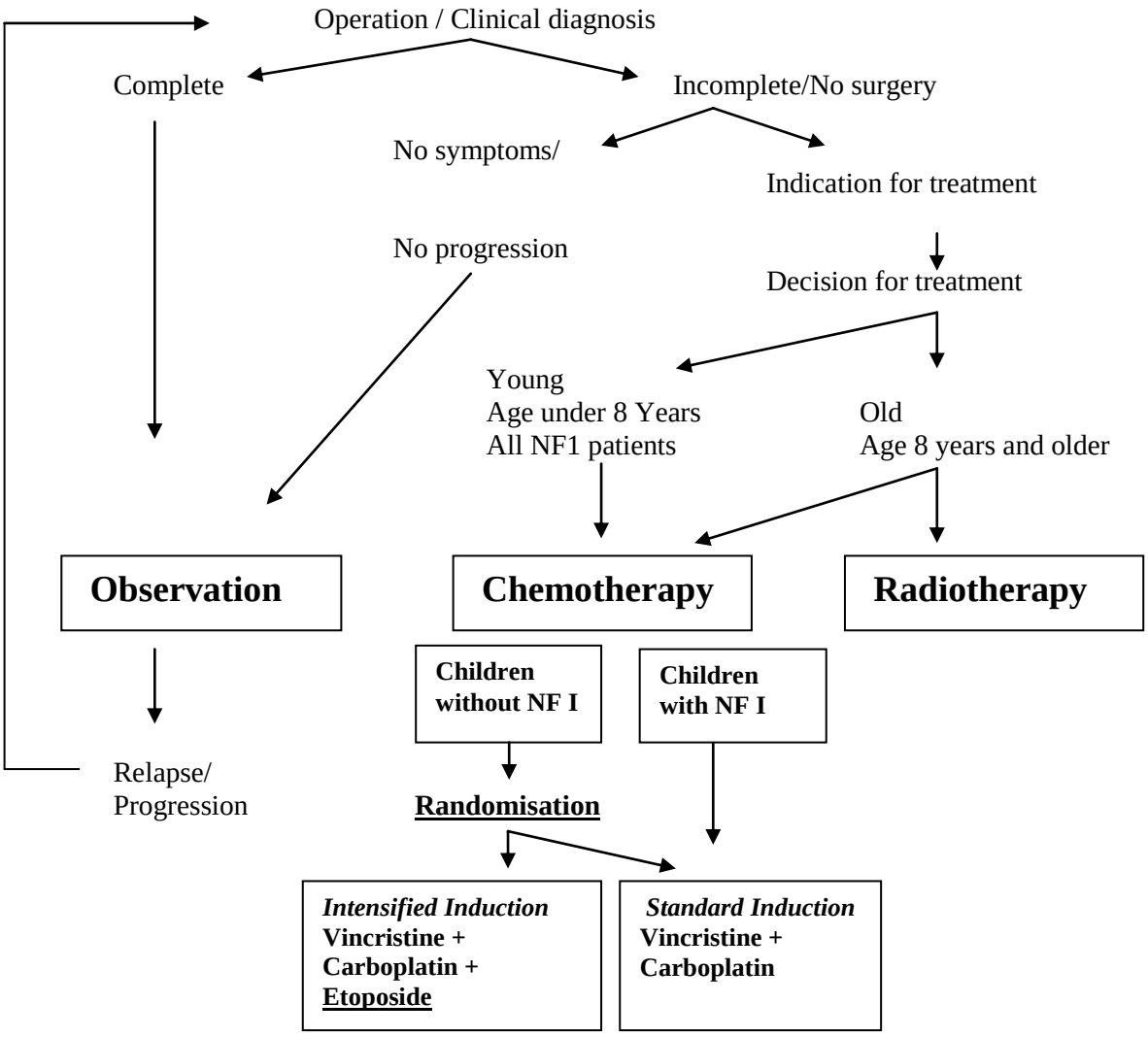
Final evaluation

The final analysis will be performed after all expected events occurred, unless the trial was stopped before.

1. Introduction

The study SIOP-LGG 2004 offers a common therapy strategy for all children and young people with a histologically or radiologically confirmed low grade glioma. For full details of the rationale and background to this protocol, please refer to **sections 3, 4 and 5 of the SIOP-LGG protocol (pages 25-59).**

2. Study Outline



3. Aims of the Study and Study Questions

Refer to the **SIOP-LGG protocol sections 6 and 7 (pages 60-62).**

4. Eligibility Criteria

Refer to **section 9 of the SIOP-LGG protocol (pages 82-83).**

- Age: children and young people up to the age of 25 years (25th birthday)
  - Patients aged from 16 up to the age of 18 years (18th birthday) are eligible for non-randomised treatment and observation
  - Only patients with pilocytic histology aged from 18 up to the age of 25 years (25th birthday) are eligible for non-randomised treatment and observation
  - Patients aged 18 and over with WHO grade 2 histology are recommended to enter the EORTC study BR13 (EORTC 22033-26033)
- Histology: glioma of low grade malignancy (ICD O-Code)

Pilocytic Astrocytoma I°	9421/1
Subependymal Giant Cell Astrocytoma I°	9384/1
Dysembryoplastic Neuroepithelial Tumor I°	9413/0
Desmoplastic Infantile Ganglioglioma I°	9412/1
Ganglioglioma I° and II°	9505/1
Pleomorphic Xanthoastrocytoma II°	9424/3
Oligodendroglioma II°	9450/3
Oligoastrocytoma II°	9382/3
Astrocytoma II°	9400/3
Fibrillary Astrocytoma II°	9420/3
Protoplasmatic Astrocytoma II°	9410/3
Gemistocytic Astrocytoma II°	9411/3

All histological subtypes will be included in the randomisation, since up to now there is no data to exclude any of the subtypes (e.g. children with oligodendroglioma), from this study. Children with chiasmatic-hypothalamic tumours may be eligible without histological diagnosis, if neuroradiological findings are consistent with a low grade glioma at this site.

- Site: intracranial and/or spinal cord primary site
- Extent: localised or disseminated tumour
- Associated conditions: children are eligible for the trial regardless of the presence of associated genetic disease
- Written informed consent
- National and local ethical and regulatory approval

5. Eligibility for Randomisation

All patients up to the age of 16 years (16th birthday) without NF1 receiving chemotherapy as their first non-surgical treatment are eligible for randomisation.

Central radiological and central pathology review is mandatory for the randomised patients.

6. Exclusion Criteria

- **Primary tumour localisation:** Diffuse tumours of the pons, even if histologically an Astrocytoma I^o or II^o is diagnosed.
  Exception: pontine glioma II^o in NFI patients may be entered into the study.

- **Special diagnosis:** Patients presenting with rare intracranial neoplasms of low grade malignancy, but of non-glial origin may be treated according to this protocol but will not be included in the randomised trial. Their data may be registered however, to learn about those therapeutic interventions which may prove useful to these patients and to develop strategies in the future. Choroid plexus papilloma should be entered on the SIOP-CPT study.

- **Previous treatment:** Patients who have had treatment with chemo- or radiotherapy prior to entering the study will be evaluated separately.

- **Pre-existing impairment** of health status, making the conduct of the study impossible or ethically unwise.

- **Pregnancy or lactation period**

- **NB: Concomitant medication** for associated or other conditions (e.g. steroids, hormone replacement, anticonvulsants) should be recorded, but it is not an exclusion criteria.

7. Treatment Strategy Subgroups

The indications to start non-surgical therapy are identical for all low grade gliomas, with non-surgical therapy being either chemotherapy or radiotherapy. A first attempt at resection should be performed, if feasible, although some children will be diagnosed on radiological grounds only. These indications to start non-surgical therapy are based upon the extent of surgical resection, the presence or absence of severe neurological symptoms and the presence or absence of clinical and/or neuroradiological progression during a period of observation. These are thus three "strategy" subgroups:

- Observation group: Tumour completely resected
  Tumour not or incompletely resected, no severe symptoms
  Tumour not or incompletely resected, no progression

- Treatment group at diagnosis: Severe neurological symptoms
  Severe ophthalmic symptoms

- Treatment group after observation: Progressive neurological symptoms
  Progressive ophthalmic symptoms

Neuroradiological progression

8. Stratification of Non-Surgical Therapy

For all patients eligible for non-surgical therapy there is an age-related stratification of non-surgical treatment as follows:

- Primary chemotherapy: "young" children, age <8 years
  All children with NF1
- Primary radiotherapy: "older" children, age >8 years
  Children of all ages whose tumour is amenable to interstitial radiotherapy (brachytherapy)

9. Diagnostic Criteria of NF1

Refer to **section 12.3 of the SIOP-LGG protocol (page 106).**

10. Indication to Start Non-Surgical Therapy

Refer to **section 10 of the SIOP-LGG protocol (pages 84-86).**

Indication to start non-surgical therapy at diagnosis following subtotal or partial resection:

Severe pre-existing visual disturbance
- Borderline vision in both eyes ("threat to vision")
- Definite history of visual deterioration
- Nystagmus due to poor vision (especially in infants up to two years)

Clinical indication
- Diencephalic Syndrome
- Symptomatic metastases

Note: The presence of postoperative residual tumour is not an indication for therapy on its own.

Indication to start non-surgical therapy at diagnosis without prior tumour resection (following biopsy or radiological diagnosis):

Severe visual symptoms
- Borderline vision in both eyes ("threat to vision")
- Definite history of visual deterioration
- Nystagmus due to poor vision (especially in infants up to two years of age)

Severe neurological symptoms
- Diecenphalic Syndrome
- Focal neurological defects secondary to tumour growth
- Symptoms of increased intracranial pressure secondary to tumour growth
- (Focal) seizures secondary to tumour growth
- Symptomatic metastases

Note: The presence of a tumour is no indication for therapy on its own.

Indication to start non-surgical therapy following observation, if surgery is not feasible:

Progressive neurological symptoms
- Manifestation of new neurological symptoms
- Increase of severity of existing neurological symptoms
- Manifestation of Diecencephalic Syndrome

Progressive visual disturbances
- Reduction/loss of vision or of visual fields
- Any reduction/loss of vision in the second eye, if the other eye is blind

Neuroradiological progression
- Definite increase of tumour size (increase of the diameter of the optic nerve)
- Involvement of previously uninvolved areas of the brain
- Manifestation of tumour dissemination (including symptomatic or progressive metastases, symptomatic leptomeningeal dissemination)

11. Definitions

11.1 **Tumour size (volume) progression** – Unequivocal increase in tumour size (volume) is a criteria to start therapy. However, pilocytic astrocytoma may have solid and cystic components. If only the cystic component(s) enlarge, while the solid ones remain unchanged, this is not sufficient evidence of tumour progression, although neurosurgical intervention may be necessary to relieve symptoms of local or generalised pressure.

11.2 **Decrease in visual function** – The evidence of an increasingly compromised visual function (marked decrease of the visual acuity and/or the visual field) regardless of tumour volume changes, and in the absence of any other overt cause, should be considered a criteria for starting therapy. Clinicians have to be aware, that quite often in young children the results of the ophthalmological examinations may vary according to the child's compliance to the procedure and the tests. Thus, particularly in the face of a radiologically stable disease, any visual function changes should be confirmed by two consecutive ophthalmological tests. This is especially important for children with NF1. One of the aims of this study is to attempt to standardise tests of visual function in children, and treating clinicians should encourage their ophthalmological colleagues to use the protocol for visual assessment in children (see section 21 of UK protocol).

11.3 **Diencephalic Syndrome** – DS in itself is a clinical indication for starting therapy. The main characteristics are a progressive emaciation and failure to thrive in an apparently alert, cheerful infant. DS is usually due to a low grade glioma involving the hypothalamus. Treatment with aggressive surgery and/or radiotherapy is variably successful in controlling the disease, but may result in severe neurological sequelae. Chemotherapy seems effective in controlling the clinical symptoms despite a rather long time period until changes are seen.

11.4 **Disseminated low grade glioma at diagnosis** – The presence of multicentric, disseminated disease by itself is not necessarily an indication to start therapy, if no other criteria to initiate non-surgical therapy are met. A very careful and accurate period of clinical observation may be appropriate.

11.5 **NF1** – **Metachronous tumours –** Patients with NF1 are at risk of developing multiple (brain) tumours, especially if they present with optic pathway glioma (Friedman 1997). Such metachronous tumours have to be distinguished from secondary dissemination of a LGG. Thus, there may be an indication for non-surgical therapy for any individual tumour.

12. Treatment Groups

Depending upon primary tumour site and the presence or absence of NF1, patients are divided into three treatment groups:

12.1 **Group 1:** Children **not** affected by NF1, with a low grade glioma of supratentorial midline including:
Optic pathway/chiasmatic-hypothalamic region
Basal ganglia
Thalamus
Mesencephalon

Surgery for this group of patients has a very limited role. These patients are eligible for the randomised chemotherapy study if aged <8 years. Patients aged >8 years could be entered into the radiotherapy study or be randomised into the chemotherapy study at the patient/parent/clinician's discretion.
Refer to **section 12.1 of the SIOP-LGG protocol (pages 92-97).**

12.2 **Group 2:** Children not affected by NF1, with a low grade glioma of any other site:
Cerebral hemispheres
Cerebellum
Spinal cord
Optic nerve (intraorbital, anterior N II; Dodge I).

For this group of patients surgery plays a major role. The small subgroup of children needing non-surgical treatment are eligible for randomised chemotherapy study if aged <8 years. Focal radiotherapy can also be considered as treatment for a small tumour area in a child <8 years. For patients aged >8 years radiotherapy is the preferred first line non-surgical therapy. However, these patients could be randomised into the chemotherapy study at the patient/parent/clinician's discretion.
Refer to **section 12.2 of the SIOP-LGG protocol (pages 98-105).**

12.3 **Group 3:** Children affected by NF1, with a low grade glioma of any site.

Patients with NF1 eligible for non-surgical treatment should be treated with the standard vincristine and carboplatin arm of the protocol and are not eligible for

randomisation. They should not be irradiated unless the chemotherapy and surgery options have failed.
Refer to **section 12.3 of the SIOP-LGG protocol (pages 106-109).**

13. Preoperative Investigations

13.1 Essential investigations

1. Neurological examination

2. Ophthalmological assessment (See section 21 of UK protocol)

3. Cranial MRI without and with Gadolinium enhancement

4. Spinal MRI without and with Gadolinium enhancement – if indicated
   Indications for a spinal MRI in low grade glioma are:
   - Multiple lesions demonstrated on cranial MRI
   - Spinal (cervical) lesions seen on cranial MRI
   - Clinical symptoms that might relate to spinal lesions

5. General preoperative diagnostic procedures:
   - Complete physical examination including height and weight, assessment of NF1 status by through skin examination, symptoms of Diencephalic Syndrome or other symptoms
   - Preoperative laboratory investigations: full blood count and differential, urea, serum-creatinine, electrolytes, Magnesium, ALT/AST, Bilirubin

6. Audiogram – pure tone where possible (age 3 years or over), otherwise free field testing or otoacoustic emissions if indicated

7. Neuroendocrine investigations if indicated
   - Baseline endocrinological investigations

8. Health status, quality of life

13.2 Recommended investigations: (pre or postoperatively, depending on the condition of the child at diagnosis and if relevant)

1. Neurophysiological investigations
   - EEG
   - Extended ophthalmological investigations including visual evoked potentials (see visual assessment pilot study)

2. Neuropsychological assessment

3. Neuroendocrine investigations
   - Base line endocrinologic investigation

- Tumor-induced primary hypothalamo-pituitary dysfunction is rare in low grade glioma even in case of chiasmatic-hypothalomic localisation. It should be investigated however in all children with diencephalic syndrome, short stature or relevant clinical findings at diagnosis.
- Pregnancy has to be excluded by HCG-determination in fertile adolescent girls.

13.3 Postoperative investigations

1. Neurological examination

2. Cranial MRI without and with Gadolinium enhancement within 24 to 48 (maximum 72) hours postoperatively

3. Spinal MRI without and with Gadolinium enhancement – only if not done preoperatively, yet indicated

4. Lumbar CSF cytology – if indicated by the presence of leptomeningeal disease
   Lumbar CSF sampling will be performed only if imaging procedures demonstrate disseminated disease
   The purpose of CSF sampling is to investigate the presence of CSF neoplastic cells following cytospin. Raised intracranial pressure should be excluded prior to the procedure.
   The presence of neoplastic cells in the CSF is regarded as stage M1
   Protein level in the CSF should be recorded in a parallel fashion to follow the patients during treatment

14. Guidelines for Neuroradiological Assessment

MRI has become the preferred modality for the evaluation of pediatric brain tumours because of its non-ionising nature and superior spatial and contrast resolution. In addition, the multiplanar imaging capabilities of MRI are very valuable in defining the extent and infiltration of complex tumors. The evaluation of primary spinal tumours and CSF-dissemination of CNS tumors by MRI has replaced CT-scan assisted myelography (CAM). In exceptional cases, if MRI is unavailable or there are specific contraindications to MRI (such as metallic foreign bodies), CAM can be used as a substitute. If MRI scanning cannot be undertaken due to lack of local availability of this resource, consideration should be given to transferring the patient to another centre for diagnosis/management. If postoperative examination can only be done by CT-scan (because of access to MR scanning), MRI scanning should be scheduled as early as possible.

14.1 Minimal requirements for <u>cranial</u> MRI

SINCE MRI IMAGING IS PERFORMED AT MANY INSTITUTIONS, THE FOLLOWING MINIMUM REQUIREMENTS ARE DEFINED:

〉 The standard examination should consist of a T2-weighted FSE (fast spin echo) dual echo sequence preferably in the axial plane. The short echo T2-sequence may be substituted by a FLAIR-sequence. The slice thickness should not exceed 5mm and the slice factor should not exceed 20%.

〉 A T1-weighted sequence, preferably in the axial plane, should be obtained by the same scan sequence after intravenous contrast administration. Additional T1-weighted post-contrast sequences in the coronal and sagittal plane are very helpful. In small or irregular tumors slice thickness should be correspondingly small.

Conventional spin echo-techniques are preferred to all kinds of gradient echo sequences, because flow-related enhancement of cerebral vessels by gradient echo-sequences may cause problems in differentiation from meningeal enhancement and the extent and degree of enhancement may be of a lesser degree than conventional T1-weighted imaging.

〉 On all images a ruler (graticule scale) must be shown.

〉 Generally, follow-up scanning should be comparable with prior examinations as it can be very hard to make direct comparisons between studies using different imaging planes and machines.

14.1.1 Application of contrast media

The administration of Gadolinium should follow the general rule of a slow intravenous injection of 0.1mmol/kg bodyweight Gadolinium. The post-contrast scan should not be started until after the full injection of the contrast medium.
Due to the presence of different Gadolinium containing contrast-media, care must be taken to ensure that equivalent amounts of Gadolinium are always used.

14.1.2 Minimum requirements for <u>spinal</u> MRI (in case of CSF dissemination)

Indications for a spinal MRI in low grade glioma are:

- Multiple lesions demonstrated on cranial MRI
- Spinal (cervical) lesions seen on cranial MRI
- Clinical symptoms that might relate to spinal lesions

〉 The minimum requirement is a post-contrast T1-weighted sagittal sequence of the entire spinal canal (down to at least S2 as the thecal sac usually ends there, but may be even longer). Slice thickness should be no more than 3mm thick and the slice factor should not exceed 10%. Axial T1-weighted images should be obtained through any areas of equivocal enhancement, employing a slice thickness of not more than 4mm (slice factor may vary according to the volume to be covered).
In many cases the normal enhancement of intradural veins covering the conus and distal cord can be mistaken for pathological leptomeningeal enhancement if only sagittal scans are available. Additional axial T1-weighted post-contrast imaging of this region is often necessary and helpful in evaluating this region.

〉 T2-weighted sequences are rarely required for the evaluation of CSF-dissemination. If necessary, they can be added after the T1-weighted post-contrast MRI has been acquired. Fast spin echo sequences are preferred because they show less CSF-pulsation artifacts.

〉 Metastatic disease on imaging is defined as the presence of nodular leptomeningeal and/or sub-ependymal enhancing nodules or of a diffuse leptomeningeal enhancement.

14.1.3 Postoperative radiological investigation of primary tumour

MRI is the imaging modality of choice. Scanning should be undertaken within 48 hours following surgery to minimise the effects of reactive post-surgical enhancement. Every effort should be made to establish whether foreign material such as surgical or chemotherapeutic wafers was placed in the surgical bed. The same sequence parameters should be employed as in the pre-operative diagnostic study to facilitate comparison. CT scan is accepted in case MRI is not available and should be performed without and with contrast medium as indicated prior to surgery within a time frame of 48 hours (max 72 hours post surgery).

14.1.4 Spinal MRI after surgery

If preoperative imaging of the spinal canal in case of a possibly disseminating tumour was not performed, it can be done at any convenient time point after surgery. However, after surgery of the posterior fossa investigators have to be aware of non-specific subdural enhancement of various degrees within the spinal canal. This rarely impedes the exact definition of meningeal dissemination, but must not be misinterpreted for intradural enhancement as a consequence of dissemination. Non-specific enhancement is usually most extensive immediately after surgery and diminishes thereafter.

14.2 Requirements for cranial CT scan (in case MRI is not available or contraindicated)

The gantry angulation should be adjusted to minimise direct irradiation of the lens of the eye. At least 4 to 5 mm thick contiguous sections should cover the posterior fossa and base of the skull. In the supratentorial compartment 8 to 10 mm thick sections are adequate. Ideally identical slices should be obtained after slow intravenous injection of iodinated contrast medium (up to 2 ml/kg bodyweight of 300mg/ml Iodine concentration).

14.2.1 Timing of CT scan investigations

If MRI is not available and postoperative CT scanning has to be performed, scanning should be undertaken within 48 to 72 hours of surgery. Efforts should however be made to obtain MR imaging within this time frame or as early as possible.

14.3 Imaging requirements for presumed low grade glioma

If on MRI the tumour is clearly arising from the optic nerve, tract and chiasm and is not confined to only one part of this pathway no additional imaging to MRI is required, especially if the patient has NF I.

If on MRI the tumour is arising from the chiasmal region without contiguous involvement of other structures of the optic pathways, various different processes such as germinoma or craniopharyngioma may mimic a hypothalamic glioma. Differentiation according to MRI signal intensities may not be possible. MR spectroscopy may, however, be helpful in differentiating these lesions from astroglial tumours.

Craniopharyngiomas are usually at least partly calcified. Therefore, CT scanning can be helpful for differential diagnosis as calcifications are not reliably demonstrated by MRI.

In addition, since germinomas are usually iso- to hyperdense due to their intrinsic high cellularity, pre-contrast CT-scan imaging (only covering the tumour region) can be helpful in assessing a suprasellar mass. At present it is not yet clear, if diffusion weighted MRI is able to substitute CT-scan in the assessment of the cellular density of germinomas.

14.4 Central radiological review

Central radiological review will be organized within the participating national groups. The national radiological reference centers will follow the guidelines as detailed within the protocol.

The images of any case of tumour not biopsied or resected for diagnosis should be seen by a dedicated neuroradiologist and sent in for central review. Images should be sent on a CD.

The images must be sent in for central radiological review in all children entering the randomised arm of the chemotherapy trial. Images should be sent on a CD.

For assessing response to chemotherapy or radiotherapy all relevant scans have to be sent in for review during the pre-treatment and treatment periods.

To answer the question of response distribution at week 24 following induction treatment for children entering the chemotherapy arm of the study, it is necessary to review the relevant scans centrally. Additionally evaluation of the point of "best response" throughout treatment will be assessed, for which scans shall be performed at 6-monthly intervals. Qualitative changes of contrast enhancement will be described and correlated with response.

The timeline for the central radiological review of the neuroimaging for children participating in the chemotherapy trial is as follows:

Time 1 at diagnosis

Time 2	where applicable after observation to demonstrate progression or measure changes at the time of start of chemotherapy
Time 3	six months after commencement of chemotherapy
Time 4	twelve months after commencement of chemotherapy
Time 5	eighteen months after commencement/at the end of chemotherapy
Time 6	"progression scan": scan during or after therapy showing progression

Scans will need to be centrally reviewed from time-points 1 and 2 in order to validate radiological criteria for tumour progression and to confirm radiological or diagnostic imaging criteria.

At time point 3 scans have to be reviewed to validate the response and assess the distribution of response at week 24 following induction treatment.

At time points 3 to 5 central radiological review needs to take place to validate the best response during treatment and for comparison against subsequent scans (time point 6), where progression was deemed to have occurred in order to validate the time of progression.

In all cases of neuroradiological progression during observation/before starting treatment and during or following therapy, review should confirm that the criteria for disease progression have been met (see section 16.3). Minimal or transient changes of tumour size should not be termed progressive disease. All comparisons of tumour size have to be made.

- To the size at diagnosis for those being observed
- To the size at start of therapy to assess treatment response at the defined time points
- To the size at "best response" for subsequent assessment of tumour status for those having been treated

Minimum required sequences for central radiological assessment:

	Cranial MRI preoperatively	Cranial MRI postoperatively 24-48 (-72) hrs and follow-up	Spinal MRI
PD or Flair	X	X	-
T 2 axial	X	X	-
T1 without Gd	X (axial)	X (axial)	
T1 with Gd	X (axial)	X (axial)	X (sagittal)
T1 with Gd (additional planes)	X (coronal or sagittal)	X (coronal or sagittal)	X (axial in areas of suspicious enhancement)

15. Surgical Guidelines

Refer to **section 13 of the SIOP-LGG protocol (page 112-115).**

The strong association between the extent of resection and progression free survival favours radical surgery, at least for hemispheric, cerebellar and intramedullary tumours. But, a number of low grade gliomas, like dysembryoplastic neuroepithelial tumors and gangliogliomas, remain quiescent even after incomplete resection. Surgical strategies are generally made based on individual decisions, however some recommendations may be useful to define the role of surgery within the treatment concept.

Recommended considerations:

1. During the surgical procedure tumour tissue should be sampled not only for conventional histology, but for the tumour tissue bank for future biological investigations.

2. Early postoperative imaging is important to determine the extent of resection. **See section 14.1.3 of UK protocol for radiological details.**

3. If postoperative imaging discloses that a potentially resectable lesion has been incompletely removed, second surgery should be considered for gross total removal before proceeding with any adjunctive therapy.

4. To reduce surgical morbidity the use of technical adjuncts, like intraoperative ultrasound, frameless stereotaxy and neurophysiological methods, which facilitate tumour localisation and intraoperative management, is strongly recommended.

15.1 Low grade glioma of the supratentorial midline in children not affected by neurofibromatosis NF1

Management for tumours of these locations is still controversial, but the surgical procedure is determined by the answers to the following questions:

1. Can the tumour be classified by neuroradiological criteria with respect to location (located within the visual pathways) and thus to the possible low grade histology?
2. Is the tumour potentially resectable without deterioration of the clinical symptoms and without unacceptable late effects?
3. Are the space occupying effects mainly determined by a cystic part of the tumour?
4. Is the interruption of the circulation of cerebrospinal fluid due to the mass effect of the tumour?

With regard to the location of the main tumour bulk and its potential origin this group of tumours will be divided into tumours originating within the visual pathways and tumours of the hypothalamus, basal ganglia and thalamus.

15.1.1. Tumours of the visual pathways

Extensive research of optic pathway gliomas are burdened with substantial surgical morbidity with respect to vision and endocrine deficits and severe hypothalamic disturbance.

Indications to perform surgery in this group of tumours may be:

- to verify a low grade glioma histologically in cases not allowing a definite neuroradiological classification prior to the start of non-surgical therapy
- to perform a primary partial resection in cases with a symptomatic exophytic portion of the tumour, which often is partially cystic, with mass effect and hydrocephalus: e.g. from the 3rd ventricle in case of hydrocephalus or from the temporal lobe in case of epilepsy
- to perform a secondary partial resection or a biopsy upon progression during or following chemotherapy or before radiotherapy

15.1.2. Tumours restricted to the optic nerve (anterior, intraorbital portion)

Resection of unilateral optic nerve glioma should only be performed in the presence of a blind eye and progressive exophthalmus. Otherwise a cautious wait and see policy should be followed and non-surgical options should be considered.

15.1.3 Tumours of the hypothalamus, basal ganglia, thalamus and mesencephalon

In case of a radiologically circumscribed tumour there is a definite indication to perform primary surgery. However, limiting factors for the extent of resection are a bilateral extension of hypothalamic tumors, the localization of a thalamic tumour within the dominant hemisphere or bithalamic involvement. In these cases only a biopsy or limited partial resection are feasible.

Focal tumours of the mesencephalon are often resectable, at least subtotally.

In tectal gliomas of typical radiological appearance presenting with hydrocephalus due to stenosis of the aqueduct a third ventriculostomy should be performed as primary intervention. An attempt at tumour resection in typical tectal glioma is not indicated. However, if other mesencephalic tumours show progression during radiological follow-up, histological verification of a low grade glioma before non-surgical therapy is strongly recommended.

15.2 Low grade glioma of all the other sites in children not affected by neurofibromatosis NF1

The resectability of low grade gliomas of the cerebral hemispheres, the cerebellum, the caudal brain stem and the spinal cord is determined by the exact location and the radiological growth characteristics (diffuse versus focal). For

well circumscribed lesions a gross total resection should be the operative goal, if it can be achieved without major risk. Conversely, if following information from imaging, history and symptoms the differential diagnoses include the presence of a lesion not necessitating radical excision, primary stereotactical biopsy may be indicated to verify the histological nature of the process.

15.2.1 Cortical and subcortical hemispheric tumours

In these locations primary complete surgery should be the goal. Pre- and intraoperative definition of functionally important cortical regions and subcortical tracts should be integral part of the planning procedure.

15.2.2. Deep hemispheric tumours extending towards the basal ganglia

The potential resectability depends upon the extension into adjacing tracts.

15.2.3. Cerebellar tumours

Complete resection is the goal of primary surgery, which, however, may not always be possible in lesions extending into the brain stem and the cerebellar peduncles.

Besides well known coordinative and motor tasks, the cerebellum actively contributes towards high mental function by processing cognitive and linguistic or emotional and social behavior. Surgical approaches to cerebellar tumours should take these facts into account, as well.

15.2.4. Tumours of the caudal brain stem

MR-classification has subdivided tumours of the brain stem into diffuse, focal, exophytic and cervico-medullary brain stem gliomas. Complete resection should be discussed for focal lesions which may be reached without unacceptable morbidity.

- Focal tumours of the pons are rarely surgically accessible without severe surgical morbidity
- Dorsally exophytic lesions are focal tumours typically growing out of the medulla oblongata, extending into the cavity of the 4th ventricle, from where they can be resected
- In non-exophytic, focal tumours of the medulla oblongata avoidance of permanent functional impairment has absolute priority. Even modern neurophysiological monitoring during the surgical procedure cannot assure functional integrity in an attempted radical excision
- Dorsally exophytic tumours of the cervico-medullary junction can often undergo gross total resection with excellent long-term prognosis even concerning morbidity.

Diffuse intrinsic brain stem gliomas are “non-surgical” tumours, in case of typical MRI morphology there is no need for a biopsy. Since these tumours are considered of high grade malignancy regardless of the exact histological

diagnosis, children and young people with such tumours are excluded from the protocol (see section 9.2).

15.2.5 Spinal tumours

The majority of spinal intramedullary tumours in children are low grade gliomas. In the presence of focal tumours an attempt of radical resection may be performed. Multilevel laminotomy is needed for some of these extended tumours to avoid postoperative severe kypho-skoliosis. Intra-operative electrophysiological monitoring and ultrasonic aspiration of intramedullary tumours should be employed to reduce surgical morbidity.

15.3 Low grade glioma of any location in patients affected by neurofibromatosis NF1

Considering the possible diagnostic categories for tumours in various locations the following recommendations can be made:

15.3.1 Visual pathway gliomas

There is no indication for a biopsy in lesions restricted to the visual pathways. Surgical resection has to be considered with even more reserve than in children without NF1, except in rare cases with space occupying lesions.

15.3.2 Tumours restricted to the optic nerve (anterior, intraorbital portion)

Resection of unilateral optic nerve glioma should only be performed in the presence of a blind eye and progressive exophthalmus. Otherwise a cautious wait-and-see policy should be followed and non-surgical options be preferred. Since an optic nerve glioma in a NF I patient may only be the initial manifestation of a more extensive involvement of the visual pathways, resection may not prevent progression.

15.3.3 Tumours of all other locations

In case of primary contrast enhancing lesions of any other location, resection should be envisaged for all resectable or potentially life-endangering lesions, e.g. of the Foramina Monroi. Since outside the visual pathways children with NF I may develop tumours of all possible histologies, biopsy or resection have to be performed prior to the start of any non-surgical therapy.

In lesions without contrast enhancement radiological observation is recommended and surgical intervention (biopsy) should only be performed in case of unequivocal progression (MRI and/or MR-spectroscopy).

16. Histopathological Diagnosis

The acquisition of histological samples for tissue diagnosis is strongly recommended in all cases. Children with NF1 and hypothalamic/visual pathway glioma and children without NF1, whose tumour shows unequivocal contiguous involvement of the visual pathways may enter the study without biopsy.

16.1 Neuropathological guidelines

The purpose of histological assessment in these tumours is to:

- Confirm the presence of glial tumours corresponding to grade 1 or 2 (WHO) and to exclude anaplastic gliomas, glioblastomas and tumours of other histological types
- Provide a standardised classification, which will facilitate detailed clinicopathological studies, with particular reference to neuroradiological findings
- Investigate the clinical significance of proliferation indices (as determined by immunocytochemistry) in the low grade gliomas of childhood

It is recognised that the exact classification and histogenetical typing as well as the grading of low grade gliomas in childhood may present difficulties. Therefore it is indispensable that tumour material of all children, registered within the SIOP - LGG trial be classified centrally. A panel of neuropathologists will assess these tumours. Facilities for "fast- track" pathology review will be provided for cases of particular diagnostic difficulty or uncertainty.

Children entering the randomised chemotherapy trial must have central review of their biopsy specimens, if obtained.

From each patient representative, paraffin embedded tissue and the documentation form should be sent to the national brain tumour reference centre. For the UK, pathology material will be requested from centres using the CCLG CNS Pathology System (June 05), following receipt in the CRCTU of Trial Registration and Pathology Report, and then sent on for review. All material will be returned to the sender following handling and final statement, except for proof-slides that will be kept. Central pathological assessment includes conventional histological and immunohistochemical staining. In the case of unusual and diagnostically difficult tumours, members of the pathology panel and other experts should be consulted – this is outside the usual process for central pathology review. Review panel findings will be documented on a report form designed for this study and will be sent to the national/international study data centre, but will not be sent back to the local pathologist or neuropathologist. Standardised histopathological parameters of each patient will be stored in a database (German Brain Tumour Reference Centre: Database: Filemaker Pro). Study material and the database will be available for all participating colleagues.

The criteria for classification are based upon the WHO classification in its current, revised version including the grading system (Kleihues 2000).

16.2 National brain tumour reference centres:

United Kingdom:

Keith Robson	Dept of Pathology, Queen's Medical Centre, Nottingham, NG7 2UH
James Ironside	National Surveillance CJD Unit, The Bryan Matthews Building, Western General Hospital, EDINBURGH, EH4 2XU

16.3 Neuropathology – laboratory guidelines

Besides warranting a uniform neuropathological diagnosis, a series of cytological, histological and immunophenotypical parameters shall be raised and documented from the materials sent in. A goal of these investigations is to identify parameters of prognostic significance.

16.3.1 Conventional histology

All biopsy specimens for histological evaluation should be fixed in formalin (preferably 10% neutral buffered formalin) and embedded into paraffin wax. Since it is anticipated that many of the histological specimens for this study will be derived from stereotactic biopsy specimens, the material for review will sometimes be limited. The material requested for histological review consists of:

- 4 unstained paraffin embedded sections 5-6m in thickness and cut onto poly-l-lysine coated slides (or equivalent) to facilitate immunocytochemistry
- The original paraffin block (if possible)
- The pathology report from the original hospital, along with patient details including the age of the patient and site of biopsy

16.3.2 Investigations to be performed:

- Staining with haematoxylin and eosin for standard morphological assessment
- Immunocytochemistry for glial fibrillary acidic protein and others as needed
- Immunocytochemistry of the cellular proliferation rate of the tumour (e.g. by means of an antibody directed against an epitope of the Ki67/MIB-1-antigen).
- Immunohistochemical investigation of differentiation antigens such as neuronal markers
- Evaluation of characteristic histological parameters (certain growth patterns, patterns of vascularisation, infiltration with inflammatory cells)

Proof slides submitted in to study will be retained for purposes of central review at least until the study is completed.

16.3.3 Scientific investigations

Knowledge concerning molecular pathogenesis of paediatric malignant glioma is scant as compared to the more frequent adult glioma. However, a large proportion of molecular investigations is only possible with unfixed, shock-frozen material. Therefore additional investigations will be done for limited numbers of patients only, although an increasing number of investigations may be performed on paraffin embedded tissue. It is an aim of the study to obtain fresh frozen material for molecular pathological studies from as many patients as possible.

Patients/parents have to consent to the use of tumour material for these investigations. Tumour material should be prepared in a standardised manner together with the local pathologist/neuropathologist and registered with the CCLG National Tumour Bank using Tissue Registration Forms, which are available at the paediatric oncology units.

16.4 UK procedure for rapid central pathology review

Rapid central pathology review should take place for those patients for whom entry into the randomised study is sought but in whom the diagnosis, made in histology, is in doubt. The process for this is direct contact between referring pathologist and one of the review panel pathologists.

16.5 UK procedure for routine central pathology review

Routine central pathology review using the CCLG CNS Pathology System (June 05) should take place for all patients in whom the diagnosis was made by histology.

17. Chemotherapy Protocol

Patients in the treatment strategy subgroup with an indication to start non-surgical therapy (see section 10 of UK protocol) who are stratified to primary chemotherapy (less than 8 years of age or all patients with NF1) should proceed to chemotherapy. All eligible patients without NF1 receiving chemotherapy as their first non-surgical treatment are eligible for randomisation of induction chemotherapy.

17.1 Assessment during chemotherapy (refer to section 8.4 of SIOP-LGG protocol pages 68-71)

1. Prior to each chemotherapy course:

- History

- Complete physical and neurological examination, including height and weight
- Laboratory data: full blood cell count and differential; urea, serum, creatinine, eletrolytes, Mg^{++} and CA^{++}, ALT/AST; Bilirubin.

2. Cranial contrast enhanced MRI

   For children receiving chemotherapy, the relevant time points for assessment of cranial MRI are:

Time 1	at diagnosis (MANDATORY)
Time 2	where applicable after observation to demonstrate progression or measure changes at the time of start of chemotherapy
Time 3	six months after commencement of chemotherapy (MANDATORY)
Time 4	twelve months after commencement of chemotherapy
Time 5	eighteen months after commencement/at the end of chemotherapy
Time 6	scan of those obtained at six monthly intervals until progression

3. Spinal contrast enhanced MRI, if previously involved at the same time points as 2.

Central review: For assessing response to chemotherapy in the randomised arms of the chemotherapy study all relevant scans have to be sent in for review **(see section 14.4 of UK protocol)**

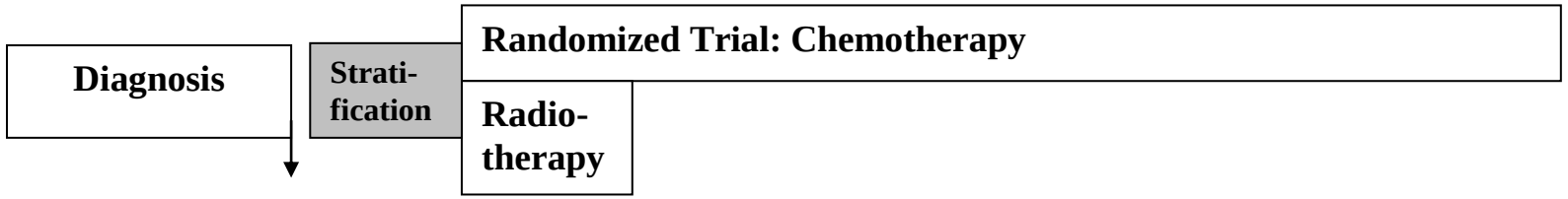
4. CSF sampling to be performed only in case of disseminated disease and if previously positive

5. Ophthalmological examination: every three months during chemotherapy

6. Glomerular filtration rate (GFR) as measured by creatinine and/or 51 Cr-EDTA clearance every six months during chemotherapy

7. Audiogram – pure tone where possible (age 3 years or over), otherwise free field testing or otoacoustic emissions every six months during chemotherapy

2.2. Flow diagram for investigation and treatment – Chemotherapy arm



Investigations:

Neuroimaging: Chemo- and Radiotherapy group

Time point	**1**	**2**		**3**		**4**		**5**	**6**
Histology (if obtained)	**X**	**(X)**							
Ophthalmology	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**
Endocrinology	**X**	**X**		**X**		**(X)**		**X**	**X**
Patient status	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**
Months after start of treatment		0	3	6	9	12	15	18	follow-up

Documentation:

Basic patient data
Central pathologic review and/or
Central neuroradiologic review
Ophthalmology
Neurology
Endocrinology
Education

Randomisation

Basic treatment data

Chemotherapy trial: Central Response assessment week 24

Chemotherapy documentation

Radiotherapy documentation

Documentation during treatment: neuroimaging, ophthalmology, neurology, endocrinology, status
At month: (3) **6** (9) **12** (15) **18**

Patient status report

If applicable:
Event report form

Post treatment:
Ophthalmology
Neurology
Endocrinology
Education
Late effects

17.2 Chemotherapy – guidelines

For dose modifications following toxicity please refer to section 14.2.3 of the SIOP-LGG protocol pages 129-131.

- For all children chemotherapy consists of an **induction period** with a more intense schedule **from week 1 to 10** and a less intense phase **from 13 to 21** and a prolonged **consolidation** therapy starting at **week 25 up to week 81, with alternative consolidation in case of allergy or early progression.**
- Due to the fact that tumour response to chemotherapy occurs at a slow pace in low grade glioma the relevant **response assessment to induction therapy is timed at week 24.**

Patients in treatment groups 1 and 2 (i.e. those without NF1) will be randomised between induction chemotherapy of vincristine and carboplatin versus a more intensive induction consisting of etoposide, vincristine and carboplatin.

Patients in study group 3 (patients with NF1) will not be randomised and are to be treated with vincristine and carboplatin chemotherapy for induction and consolidation.

Children with disseminated low grade glioma are part of one of the three treatment groups according to the location of the main/primary tumour and the absence or presence of NF1. Therefore those patients in treatment groups 1 and 2 are eligible for randomisation.

Example flowcharts for standard therapy, intensified therapy, and alternative consolidation have been provided in Appendix 1 to guide you through the patient's treatment plan and to document the administration of chemotherapy. The flowcharts may be adapted to suit your local practice.

17.2.1 Standard induction therapy

Standard induction consists of vincristine weekly and carboplatin three weekly for ten weeks as in the previous SIOP trial. Following the ten week induction treatment the combination of vincristine and carboplatin is given three times at four week intervals to allow for recovery from haematological and/or neurological side effects of the induction phase.

Treatment response evaluation by neuroimaging has to be performed at week 24.

The recommendations of the UK Chemotherapy Standardisation Group is to dose on surface area using the body surface area dosing chart produced by the group.

- Children aged less than 6 months — Give 50% dose
- Children aged 6 months to one year — Give 75% dose
- **Patients over 12 months of age who are under nourished (particularly if suffering from Diencephalic syndrome) and who weigh <10kg can be given 75% doses with the aim to increase to 100% once the nutritional state improves**
- **Please note there is NO dose reduction for young children of etoposide**

Vincristine
Vincristine is given weekly as an iv-bolus at a dose of 1.5 mg/m²/day on day 1 of week 1, 2, 3, 4, 5, 6, 7, 8, 9 and 10 and then week 13, 17 and 21 (maximum single dose: 2 mg).

Children aged less than 6 months	Give 0.75 mg/m^2 vincristine
Children aged 6 months to one year	Give 1.125 mg/m^2 vincristine

Carboplatin
Carboplatin is given as an intravenous 1-hour-infusion at a dose of 550 mg/m²/day on day 1 of week 1, 4, 7 and 10, and then week 13, 17 and 21

Children aged less than 6 months	Give 275 mg/m^2 carboplatin
Children aged 6 months to one year	Give 412 mg/ m^2 carboplatin

Standard Induction

1	2	3	4	5	6	7	8	9	10		13	17	21	24	weeks
V	**V**	**V**	**V**	**V**	**V**	**V**	**V**	**V**	**V**		**V**	**V**	**V**		
C			**C**			**C**			**C**		**C**	**C**	**C**		
														MRI	

V	**Vincristine**	1.5 mg/m² (max. 2 mg)	iv-bolus - d 1
C	**Carboplatin**	550 mg/m²	1h infusion – dl

17.2.2 Intensified Induction Therapy

Intensified induction consists of Vincristine weekly and Carboplatin and Etoposide three-weekly for ten weeks as in the previous SIOP-trial. Following the 10 week-induction treatment the combination of Vincristine and Carboplatin is given three times at four week intervals to allow for recovery from haematological and/or neurological side effects of the induction phase. Treatment response evaluation by neuroimaging has to be performed at week 24.

Vincristine
Vincristine is given once weekly as an iv-bolus at a dose of 1.5 mg/m²/day on day 1 of week 1, 2, 3, 4, 5, 6, 7, 8, 9 and 10 and then week 13, 17 and 21 (maximum single dose: 2 mg)

Children aged less than 6 months	Give 0.75 mg/ m^2 vincristine
Children aged 6 months to one year	Give 1.125 mg/m^2 vincristine

Carboplatin
Carboplatin is given as an intravenous 1-hour-infusion at a dose of 550 mg/m²/day on day 1 of week 1, 4, 7 and 10, and then week 13, 17 and 21

Children aged less than 6 months	Give 275 mg/ m^2 Carboplatin
Children aged 6 months to one year	Give 412 mg/m^2 Carboplatin

Etoposide
Etoposide is given as an intravenous 1-hour infusion at a dose of 100 mg/m²/day on day 1 to 3 of week 1, 4, 7 and 10 (no dose adaptation for children < 10 kg body weight).

Intensified Induction

1	2	3	4	5	6	7	8	9	10		13	17	21	24	week
V	**V**	**V**	**V**	**V**	**V**	**V**	**V**	**V**	**V**		**V**	**V**	**V**		
C			**C**			**C**			**C**		**C**	**C**	**C**		
Ex3			**Ex3**			**Ex3**			**Ex3**						
														MRI	

V	**Vincristine**	1.5 mg/m² (max. 2 mg)	iv-bolus - d 1
C	**Carboplatin**	550 mg/m²	1h infusion - d 1
E	**Etoposide**	100 mg/m²	1h infusion - d 1-3

17.2.3 Consolidation therapy

Consolidation consists of vincristine and carboplatin. However, treatment is prolonged up to week 81 by extending treatment intervals to six weeks and vincristine is given at a more intense schedule on day 1,8 and 15 of each cycle.

Vincristine
Vincristine is given as an iv-bolus at a dose of 1.5 mg/m^2/day on day 1 of week 25 to 27 31 to 33, 37 to 39, 43 to 45, 49 to 51, 55 to 57, 61 to 63, 67 to 69, 73 to 75 and 79 to 81 (maximum single dose: 2mg).

Children aged less than 6 months	Give 0.75 mg/ m^2 vincristine
Children aged 6 months to one year	Give 1.125 mg/m^2 vincristine

Carboplatin
Carboplatin is given as an intravenous 1-hour-infusion at a dose of 550 mg/m²/day on day 1 of week 25, 31, 37, 43, 49, 55, 61, 67, 73 and 79

Children aged less than 6 months	Give 275 mg/ m^2 Carboplatin
Children aged 6 months to one year	Give 412 mg/m^2 Carboplatin

25	31	37	43	49	54	week
55	61	67	73	79	85	
VVV	**VVV**	**VVV**	**VVV**	**VVV**		
C	**C**	**C**	**C**	**C**		
					MRI	

V	**Vincristine**	1.5 mg/m² (max. 2mg)	iv-bolus d1, 8, 15 of each 6 week cycle
C	**Carboplatin**	550 mg/m²	1h infusion d1 of each 6 week cycle

17.2.4 Consolidation therapy following allergy or early progression

Refer to section 14.2.5 of SIOP-LGG protocol (pages 131-132). Due to its allergic potential, prolonged treatment with carboplatin may not be possible. Since on the other hand, an extended treatment period may carry the potential for an extended progression free interval, total treatment time should be maintained, thus avoiding the necessity for early radiation. Alternative chemotherapy combinations shall be tested within such a continuation schedule.

The two combinations shall be given a maximum of 5 times each (i.e. 10 x 6 week chemotherapy cycles in total) to limit cumulative doses, however treatment must not continue beyond week 81 from the start of chemotherapy.

NB: stop at week 81 <u>or</u> after 10 x 6 week cycles of alternative chemotherapy, whichever comes first.

Vincristine
Vincristine is given as an iv-bolus at a dose of 1.5 mg/m²/day on day 1, 8 and 15 of each 6 week cycle starting with the first cycle post manifestation of allergy (i.e. weeks 1, 7, 13, 19, 25, 31, 37, 43, 49, and 55) (maximum single dose: 2 mg)

Children aged less than 6 months	Give 0.75 mg/ m^2 vincristine
Children aged 6 months to one year	Give 1.125 mg/m^2 vincristine

Cisplatin is given as an intravenous 3-hour-infusion at a dose of 30 mg/m²/day on day 1 and 2 of week 7, 19, 31, 43 and 55

Children aged less than 6 months	Give 15mg/m^2 cisplatin per day
Children aged 6 months to one year	Give 22.5mg/m^2 cisplatin per day

Cyclophosphamide is given as an intravenous 1-hour infusion at a dose of 1500 mg/m²/day on day 1 of week 1, 13, 25, 37 and 49

Children aged less than 6 months	Give 750 mg/ m^2 cyclophosphamide
Children aged 6 months to one year	Give 1125 mg/m^2 cyclophosphamide

Week post manifestation of allergy or early progression (maximum 5 cycles each):

1	7	13	19	25	31	37	43	49	55
VVV Cyc	**VVV Cisx2**	**VVV Cyc**	**VVV Cisx2**	**VVV Cyc**	**VVV Cisx2**	**VVV Cyc**	**VVV Cisx2**	**VVV Cyc**	**VVV Cisx2**

V: **Vincristine**	1.5 mg/m² (max 2 mg)	iv-bolus	d1, 8, 15 of each 6 week cycle
Cis: Cisplatin	30 mg/m²	3h infusion	d1 and 2 of each cycle
Cyc: Cyclophosphamide	1500 mg/m²	1h infusion	d1 of each cycle

17.3 Recommended chemotherapy administration

Vincristine IV bolus

Carboplatin IV infusion in 5% dextrose over one hour

The following fluid volumes are suggested but these are not critical and can be adjusted to the child's fluid requirements. The dextrose concentration must be greater than 0.5mg/ml.

Dose	Volume of Dextrose
25 to 250mg	50ml
251 to 500mg	100ml
501 to 1000mg	250ml

Etoposide IV infusion in 0.9% Sodium Chloride over 1-4 hours depending on the volume of infusion

Etoposide is administered in Sodium Chloride 0.9% at a final concentration less than or equal to 0.4mg/ml. Suggested fluid volumes are:

Dose	Volume of Sodium Chloride 0.9%
0 to 40mg	100ml
40 to 50mg	150ml
50 to 100mg	250ml
100 to 200mg	500ml
200 to 300mg	750ml
>300mg	1000ml

Cisplatin

Day One
T= 0 hours.
Pre hydration:
3 hours pre hydration with sodium chloride 0.9% at 200ml/m^2/hr (no maximum)

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 dose of mannitol 0.5g/kg over 15 to 30 minutes and additional fluid of 10ml/kg.

Do not give frusemide as this may impair renal cisplatin clearance.

T = 3 hours

Hydration during and for six hours post cisplatin (i.e. infuse over 9 hours)

- 2.5% dextrose/0.45% saline
- Plus 6g mannitol per 500ml
- Plus 10mmol potassium chloride per 500ml
- Run fluid at 125 ml/m^2/hour (Total fluid volume 1125 ml/m^2)

Hydration should be in a separate bag from the cisplatin and the two can 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 3 hours
- Cisplatin 30 mg/m^2 in 0.9% saline over 3 hours.
- Suggested volume of 0.9% saline for infusion:
- < 50mg in 100ml
- 50 to 100mg in 150ml

T=12 hours

Hydration for the subsequent 12 hours
- 2.5% Dextrose/0.45% saline
- Plus 10mmol potassium chloride per 500ml
- Plus 5mmol magnesium sulphate per 500ml
- Plus 0.3mmol calcium gluconate per 500ml
- Run fluids at 125 ml/m2/hr (total volume 1500 ml/m^2, maximum volume 2250ml)

Day Two
T= 0 hours.

Pre hydration:
3 hours pre hydration with sodium chloride 0.9% at 200ml/m^2/hr (No maximum)

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 dose of Mannitol 0.5g/kg over 15 to 30 minutes and additional fluid of 10ml/kg.
Do not give frusemide as this may impair renal Cisplatin clearance.

T = 3 hours

Hydration during and for six hours post Cisplatin (i.e. infuse over 9 hours)

- 2.5% dextrose/0.45% saline
- Plus 6g Mannitol per 500ml
- Plus 10mmol potassium chloride per 500ml
- Run fluid at 125 ml/m^2/hour (Total fluid volume 1125 ml/m^2)

Hydration should be in a separate bag from the Cisplatin and the two can 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 3 hours

- Cisplatin 30 mg/m^2 in 0.9% saline over 3 hours.
- Suggested volume of 0.9% saline for infusion:
- < 50mg in 100ml
- 50 to 100mg in 150ml
- >100mg in 250ml

T=12 hours

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

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

Cyclophosphamide IV infusion over 1 hour in 0.9% Sodium Chloride

Hydration 2.5% Dextrose/ 0.45% Saline 125ml/m^2/hour with mesna at 120% of the prescribed cyclophosphamide dose. Commence the infusion 3 hours prior to the cyclophosphamide infusion and continue for a minimum of 12 hours after completion of cyclophosphamide.
Suggested infusion volumes for Cyclophosphamide:

Cyclophosphamide dose	Volume of Sodium Chloride 0.9%
0 to 1000mg	50ml
1000mg to 2000mg	100ml
2000mg to 3000mg	150ml
> 3000mg	250ml

18. Radiotherapy Protocol

18.1 Indications for RT

Aged 8 years and older, treatment at diagnosis:

Severe neurological symptoms
Severe ophthalmic symptoms

Aged 8 years and older, treatment after observation:

Progressive neurological symptoms
Progressive ophthalmic symptoms
Neuroradiological progression

18.2 Timing of Radiotherapy

Treatment should commence within six weeks of surgery for patients receiving postoperative RT. For patients not appropriate for surgery, then treatment should start within six weeks of the decision to deliver RT.

18.3 Diagnostic Imaging

In order to assess the precise extent of tumour growth MR scanning including contrast enhanced T1, T2 weighted or 'flair' imaging is necessary. For treatment planning preoperative and postoperative imaging is necessary. For spinal tumours MR imaging pre- and postoperatively is indispensable to delineate extent of disease.

18.4 Treatment technique/intracranial and spinal sites

18.4.1 Intracranial sites

It is necessary to minimise the volume of normal tissue exposed to a high RT dose. Computer assisted treatment planning is therefore mandatory. Three dimensional planning should be used if possible. Conformal techniques will help to further reduce irradiation of normal tissue. In addition, the dose to critical organs must be recorded (see documentation sheets). Whenever feasible image fusion of diagnostic MRI and CT-scans should be used to determine the target volume. The use of Intensity Modulated radiotherapy (IMRT) is permitted if considered appropriate for individual patients.

18.4.2 Spinal sites

Computer assisted treatment planning should be used in order to obtain a reproducible dose distribution.

18.4.3 Target volumes

Target volumes will be defined according to the ICRU 50/62. The CTV encompasses the visible tumor as seen on MR (T2 weighted or flair images) with an additional margin of 0.5 cm. If surgery was performed, postoperative delineation of residual disease will be used for treatment planning. The preoperative scans are used to

identify regions of possible tumor infiltration. It is not necessary to entirely encompass areas of cerebral oedema. The PTV encompasses the CTV with an additional margin according to the precision of treatment technique (e.g. 0.2 - 0.5 cm if rigid head fixation and 0.5 - 1.0 cm if a conventional face masks/head shell is used) depending on departmental policy. When defining CTV anatomical boundaries (e.g. skull) should be taken into account.

For spinal sites the margin for CTV in the cranio-caudal direction should be the length of one vertebral body. It is not necessary to entirely encompass a syrinx if present or the entire zone of oedema. Postoperative imaging should be used in case of surgical resection. Laterally the field border should encompass the pedicles.

18.4.4 Dose specification

RT dose is specified according to the ICRU 50/62 report. The ICRU reference point by definition is located in the center of the target volume (100 %). Dose inhomogeneity within the target volume should not exceed the tolerance limits of 95 % and 107 %.

For spinal sites dose specification should be located at the dorsal border of the vertebrae.

18.4.5 Dose prescription

For cranial sites a total dose of 54.0 Gy should be administered in a fractionated dose of 1.8 Gy, 5 times per week. All fields should be treated daily. For spinal sites the dose is limited to 50.4 Gy.

For children under 5 years of age the dose should be limited to 45.0 Gy at 1.8 Gy per fraction.

18.4.6 Patient positioning

It is recommended that an individualised face mask (head shell) is used. An alternative would be a rigid head fixation device (e.g. GTC frame etc).

18.5 Cranio-spinal irradiation (CSRT)

Planning CT is recommended for definition of CTV for the cranio-spinal axis, posterior fossa and tumor 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 cranio-spinal axis. TVs and OAR shall be outlined:

Target Volumes (TVs)	Organs At Risk (OAR)
Craniospinal axis Metastatic deposits	Eyes Pituitary Inner ear Hypothalamus Optic chiasm

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

18.5.1 Treatment volume anatomical description and dose

Craniospinal axis:

The CTV for CRST comprises the whole brain as well as the spinal cord and thecal sac.

18.5.2 Whole brain volume

The whole brain CTV should extend anteriorly to include the entire frontal lobe and cribriform plate region. The geometric edge of the shielding block 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.

18.5.3 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 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 lower borders of the cranial fields.

18.5.4 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 scan and will usually extend inferiorly to at least the lower border of the second sacral vertebra.

18.5.5 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 foramina. The spinal CTV should extend laterally to cover the intervertebral foramina with at least 1 cm margin on either side. The use of a ‘spade’ shaped field to treat the lumbo-sacral spine is not recommended.

18.5.6 Metastatic deposits

It is strongly recommended that the CTV for metastatic deposits should be determined on a planning CT. 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 OAR where possible.

18.5.7 Dose Specification

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

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.

Metastatic deposits

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, or at the posterior aspect of the vertebral bodies for posterior fields.

18.6 Total Treatment Dose

Brain :	35.2 Gy in 22 fractions of 1.60 Gy
Spine :	35.2 Gy in 22 fractions of 1.60 Gy
Metastatic deposits : (Intracranial sites)	55.0 Gy cumulative dose , 1.8 Gy fractionated dose
Metastatic deposits : (spinal sites)	49.6 Gy cumulative dose , 1.8 Gy fractionated dose
Dose restriction (maximal cumulative dose) > 50% intracranial volume and or > 2/3 of spinal canal : 45 Gy	

18.7 Documentation

It is mandatory to document the field alignment using simulator films. At the start of radiotherapy verification films should be obtained of each irradiated field. To develop recommendations for optimal treatment techniques it is necessary to analyse the radiation protocols, the prescription of target volumes, doses and the accuracy of treatment delivery. Therefore, it is requested that the following data (copies) be sent to the reference centre for radiotherapy.

--Simulation films	
-Portal films	
-Computer assisted treatment plans	
--Evaluation forms (Addendum 21.9.)	Patient data
	Toxicity
	Treatment technique / dose prescription

18.8 Acute treatment related toxicity

Steroid prophylaxis of cerebral oedema is not mandatory during radiotherapy. If cerebral oedema occurs dexamethasone should be given orally or iv, if necessary.

The acute maximal toxicity during irradiation should be documented on the evaluation forms. The Hb level should be maintained above 10 g/dL by transfusion if necessary

18.9 Routine laboratory tests during radiotherapy

- Red and white blood cell counts, platelet counts: 2x weekly in CXA, 1x weekly in limited volume radiotherapy..
- If the patient is receiving steroid medication: blood glucose 1x weekly.
- Before and at the end of radiotherapy: sodium, potassium, calcium, GOT, GPT, Gamma-GT, LDH, creatinine, BUN, hormones of the pituitary axis (TSH, growth hormone, ACTH, FSH/LH

19. Assessment During Follow-up Observation or Following Chemo or Radiotherapy

	First, second and third year	**Fourth and fifth year**	**Sixth to tenth year**
Physical examination and neurological examination, including height and weight;	Every 3 months	Every 6 months	Annually
Laboratory data for those treated with chemotherapy Fbc, Cr, electrolytes and LFT's	Every 6 months	If indicated	If indicated
Ophthalmological assessment in patients with optic pathway glioma	Year 1: 3 monthly Year 2: 3-6 monthly Year 3: 6 monthly	Every 6-12 months	Every 6-12 months
Contrast enhanced cerebral and spinal (if indicated) MRI	Every 6 months	Every 6 months	Annually
Audiogram if post chemotherapy – pure tone where possible age 3 years or over, otherwise free field testing or otoacustic emissions	Every 6 months	Not indicated if previously repetitively normal	
Glomerular filtration rate if post chemotherapy	6 months after CT, then yearly, if not indicated otherwise	Not indicated if previously repetitively normal	
Endocrinological investigation if hypothalamic/chiasmatic tumour or received radiotherapy.	Yearly, if not indicated otherwise	As indicated by stage of growth and puberty and previous chemo- or radiotherapy	As indicated by stage of growth and puberty and previous chemo- or radiotherapy

20. Extended Endocrine Investigations and Monitoring of Growth

Depending upon tumour location, the extent of surgery and the effects of non-surgical therapy children may suffer from complex endocrine sequelae. For a summary of endocrine investigations refer to **SIOP-LGG protocol section 8.4.3 (pages 70-71)**.

21. Ophthalmological Assessment

21.1 Introduction

Children who have been diagnosed as having optic pathway and hypothalamic glioma, either with or without Neurofibromatosis Type I, require a regular and structured

ophthalmic assessment. No prospective study has tested the various types of assessment of visual function. A decision of whether to commence chemotherapy or radiotherapy is often based on optic nerve function, although there has never been a consensus regarding a structured approach to this testing.

All ophthalmic centres linked to oncology centres participating in the low grade glioma trial are encouraged to perform these tests of visual function. It is hoped that by performing these tests in a structured prospective manner it will be possible to identify which tests are the most sensitive and consequently the most useful in terms of screening children with optic pathway gliomas.

21.2 Aims

The aim of this part of the low grade glioma study is to introduce a standardised methodology of visual assessment in children of all ages with optic pathway glioma. The data will be collected in order to assess the feasibility of the tests of visual function in an international setting.

It is not possible at this stage to validate these tests, as there is no known gold standard with which to compare. Therefore patients can also be entered into a pilot study of visual function testing including the use of visual evoked potential, and comparing formal tests with subjective assessment of visual function by the parent and patient, a vision behaviour check list and with radiology.

21.3 Tests of visual function

Children should be assessed through a combination of direct and indirect testing pertinent to their ages. The modalities for testing come under the following headings:

1. Visual acuity
2. Visual fields
3. Colour vision
4. Contrast sensitivity
5. Ocular motility assessment
6. Pupil responses
7. Fundoscopy

21.3.1 Visual acuity

Visual acuity testing should be recorded using a Logmar chart which, with matching cards, can be used in children as young as 2 ½. The Logmar chart can be used either as a letter format or as LEA symbol format. For children under 2 ½ or in those where there are communication problems or other difficulties, acuity card preferential looking should be used. Visual acuity is graded from 8 (best) to 1 (worst):

Grade	LOGMAR/LEA	PL (c/d)
8	0-0.2	≥19.5
7	0.3-0.4	14.2-9.8
6	0.5-0.7	7.5-4.8
5	0.8-1.0	3.6-2.4

4	1.1-1.3	1.8-1.2
3	Hand/Toy movement	
2	Perception of light	
1	No perception of light	

21.3.2 Visual Fields

Formal perimetry should be carried out in children who are old enough to co-operate with the test. Certainly children over the age of 6 or 7 should be able and sometimes younger children can also comply. Goldmann visual fields using an experienced examiner are often both more accurate and more possible than static perimetry using an automated system. In young children confrontation testing using a toy or bright object and two examiners is a better technique. Visual field assessment is also graded on an 8-part scale:

Grade	Achievement
8	Monocular Full
7	Monocular Quadrantic
6	Binocular Quadrantic
5	Monocular Hemionopic
4	Binocular Hemionopic
3	Monocular Hemi and Quadrantic
2	Binocular Hemi and Quadrantic
1	Total Loss

21.3.3 Colour Vision

The PVC 16 colour vision testing system is likely to be the best option for testing children in this patient group. There is a reduced version of the Farnsworth 100 hue test, which involves a child matching colours. Depending how accurately these colours are matched colour vision can then be assessed and consequently graded. The Isschihara plate system is a historical test, which was devised primarily to identify patients with red/green colour-blindness. The axis of colour loss in children with optic nerve pathology is more likely to be in the blue-yellow spectrum and as a result the Ishihara test is not particularly useful. The grading system for colour vision using the PVC 16 test can be used:

PV 16	*Colour Test*
Grade	*Chart Results*
8	*Colour Circle complete*
7	*Close caps confused*
6	*One crossing of circle 7 <--> 15*
5	*Up to 2 crossings (other than 7 <-> 15)*
4	*Up to 4 crossings (other than 7 <-> 15)*
3	*5 crossings (other than 7 <-> 15)*
2	*6 crossings (other than 7 <-> 15)*
1	*7 crossings (other than 7 <-> 15)*

Defect Axis	*Protan / Deutan / Tritan / Mixed (please indicate)*

Additional Guidance for
Grading Colour Vision using Panel 16 Colour Vision Test

- Use appropriate method for age of child
- Test on a white background and use the same illumination at each test
- Use masking discs whenever possible, as this stimulates a smaller area of retina, and therefore picks up defects more easily
- Test monocularly
- Record on the colour circle chart provided with the test
- In children this test exposes confusion of colours in the Protan,Deutan, and Tritan axes
- Colour vision defects are shown on the chart as crossings of the colour circle
- Minor confusions around the circle are considered within normal limits.
- Crossing from 7 ↔ 15 is also considered normal
- More than 4 crossings on a definitive axis, is considered abnormal
- We should be looking for changes in results on retests (N.B. there may be an initial improvement on 1st retest, due to the "learning curve")

The examiner should also document the principal colours that are predominately missed (blue, red, green etc.).

21.3.4 Contrast Sensitivity

There is evidence that contrast sensitivity testing can be used to pick up subtle changes in optic pathway function and as such should be incorporated into a standard screening protocol for these children. Contrast sensitivity develops at a faster rate than visual acuity during the first 30 weeks of life. Contrast sensitivity testing has been shown to be more sensitive than acuity, field and colour vision testing in optic neuropathy. It has also proved helpful in-patients with visual pathway glioma. (Day 1997)

The VISTECH vision contrast system or the LEA contrast sensitivity test should be used on all children. With the LEA matching cards it should be possible to test children down to 2 ½ to 3 but the VISTECH system may be difficult in children under the age of 4. Using the VISTECH vision contrast test there is again a grading system on an 8-part scale:

Grade	Column "A" (1.5 c/d)
8	Grating 8
7	Grating 7
6	Grating 6
5	Grating 5
4	Grating 4
3	Grating 3
2	Grating 2
1	Grating 1

Gradings for Lea Contrast Sensitivity:

	VA -0.2 to 0.175 Log MAR test at 3M	VA 0.2 to 0.475 Log MAR test at 3M	VA 0.5 - 0.775 Log MAR test at 1M	VA 0.8 to 1.0 Log MAR test at 1M
Grade	No of Symbols seen	No of Symbols seen	No of Symbols seen	No of Symbols seen
8	25 - 22	25 - 18	25 -22	25 - 16
7	21 - 18	17 - 16	21 - 18	15 - 12
6	17 - 14	15 - 13	17 - 14	11 - 10
5	13 - 10	12 - 9	13 - 10	9 - 7
4	9 - 7	8 - 6	9 - 7	6 - 5
3	6 - 4	5 - 3	6 - 4	4 - 3
2	3 - 2	2	3 - 2	2
1	1	1	1	1

Additional Guidance for Contrast Sensitivity Testing

- Essentially we should measure CHANGES in Contrast Sensitivity as "normal" has a very wide range
- Contrast Sensitivity is related to visual acuity., therefore if VA falls, then the number of C S symbols read will be reduced, however, actual CS may still be normal
- The best measure of CS with the **Lea chart** is to measure the gradient of the slope (VA against No of symbols read at specific distance) as recorded on the chart ("normal" 65° / 75°)
- For the purpose of "grading" of **Lea Chart** results, it is proposed that the attached charts are used, which are dependant on Visual acuity
- The grading for **Vistech** testing uses the lowest special frequency on the chart, to allow for poor visual acuity.
- It is not possible to note changes by comparing Lea tests with Vistech tests, therefore the same test should be used continually in individual cases.

21.3.5 Ocular motility assessment

Children with poor vision can develop strabismus and consequently recording of the presence or absence of a squint is important. There is no grading system as such for this although it should be documented whether a squint is convergent or divergent or vertical and a measurement of either the prism cover test or the prism reflection test

(this would be in degrees or prism diopters). The presence of nystagmus should be noted which will also include its orientation (horizontal, vertical or rotary) and nature (jerk, pendular etc).

21.3.6 Pupil responses

All children should be assessed for a relative afferent pupilary defect. This is achieved using the swinging flash light test. There is no grading for this but it should be noted if a relative afferent pupilary defect is present and if so can this defect be neutralised with neutral density filters. These filters come in an increasing density and consequently mimic a loss of luminance in the eye that is being tested. By putting these filters in front of the good eye an attempt can be made to classify the relative afferent defect in the bad one.

21.3.7 Fundoscopy

Whilst not assessing optic pathway function the appearance of the optic nerves is important to document. The appearance of optic atrophy should be noted.

21.4 Frequency of Examinations

The consensus statement of the NF I optic pathway glioma task force (Listernick 1997) suggests ophthalmological examinations for children with optic pathway gliomas every 3 months during the first year following diagnosis and six-monthly until 36 months and yearly thereafter. This, however, relates to surveillance and the frequency will need to increase in children experiencing visual deterioration and to children under treatment, who will need closer follow-up. During chemotherapy it has been suggested that 3-monthly investigations should take place (Lorenz 2002). The table below shows the recommended frequency of ophthalmological examination for children participating in this study.

If there is a change in a child's condition they should be returned to 3 monthly assessment for 12 months and then to 3-6 monthly and then to 6 monthly.

Recommended frequency of ophthalmological examination during treatment and follow-up (Lorenz 2002):

At diagnosis				
Surgery	before	After	2 weeks after	Each surgical intervention
Chemotherapy	before	3 monthly		During chemotherapy
Radiotherapy	before	3 monthly		After end of radiotherapy
Follow-up	1st year	3 monthly		
	2nd year:	3-6 monthly		More frequently, if indicated
	3rd year	6 monthly		More frequently, if indicated
	4th year and later:	6-12 monthly		More frequently, if indicated

21.5 Documentation

Results of these Ophthalmology tests should be documented in the Ophthlamology data form of the SIOP LGG Protocol.

22. Health status and quality of life assessment

22.1 Aims

To determine the quality of survival of children treated for low grade glioma, and compare this between different trial arms.

The secondary aim is standardisation of morbidity assessments across European paediatric brain tumour clinical trials, in order to enhance compliance and completion of data sets consequent upon familiarity of clinical teams with the system. Comparison of morbidity data between tumour groups will be possible.

22.2 Methodology

The former UKCCSG and SIOP Brain Tumour Group have agreed upon a standardised framework for monitoring of morbidity burden consequent upon the diagnosis and treatment of brain tumours (Glaser et al, 1999). This will be adapted to national structures with appropriate modifications due to developments in methodologies since its publication. Four of the original questionnaires (Strengths and Difficulties Questionnaire [SDQ], Health Utilities Index [HUI], Medical Examination Form, Medical/Educational/Employment/Social Form) will be used. Additional health-related quality of life measures will be used.

The HUI and SDQ have been widely used and are available in 7 European languages (Goodman 1994, Feeny et al 1995). Their use is supported by the SIOP Brain Tumour Group. The medical examination form and medical/employment/education/social form for patients and parents need to be adapted for individual countries as educational qualifications and support will vary. This system is being adopted in SIOP PNET 4. The same forms will be used in this study as for PNET 4.

Health-related quality of life measures are important in providing information about patients, and their parents, perception of their health and well-being. Few measures are suitably translated, and validated, for inclusion in an international study across Europe. In keeping with SIOP PNET 4, three measures will be available for this study; the PedsQL (Varni et al,1999), PEDQOL (Ravens-Sieberer and Calaminus, 1998) and the Child Health Questionnaire[CHQ] (Landgraf et al, 2000). In the United Kingdom the PedsQL will be used, whilst in Germany the PEDQOL will be the measure of choice. The CHQ is available in multiple European languages and should be adopted by other participating countries (data is only by parental proxy response). Aged 18 + years, the EORTC QLQ-C30 with brain tumour specific add-on module (Aaronson et al, 1993) is recommended for use in all countries.

22.3 Schedule of assessments

Both, medical/education/employment/social assessment and Quality of Life, should be assessed at diagnosis, 1 year, 3 years, 5 years, 10 years from diagnosis and at age 20 years.

23. Study Conduct: Practical organisation

23.1 Registration and Randomisation

This study will be conducted by means of remote data entry, organised by CINECA, an inter-university consortium in Bologna, Italy. Further details of the remote data entry system to be clarified at the UK Investigator Meeting.

23.2 Serious Adverse Events

Serious Adverse Events (SAEs), occurring after the first administration of study drug until 12 months after termination of chemotherapy, must be reported by fax immediately on knowledge of the event to the CRCTU using a separate SAE form and a faxed copy of the Remote Data Entry (RDE) SAE Form. Once the event has been checked by the UK Chief Investigator, the SAE should then be entered onto the RDE system.

A Serious Adverse Event (SAE) is any event that:

- is fatal
- is life threatening
- requires in-patient hospitalization or prolongation of hospitalization
- results in persistent or significant disability/ incapacity
- is a congenital anomaly/birth defect
- any other medically important condition such as abnormal biological or vital signs and secondary malignancies (cancer)

Events that should not be reported as a SAE include:

- Deaths due to progression of disease that occur more than 30 days after the last protocol treatment.
- Grade 4 toxicities, except for the following categories, unless any other criteria are met:
  - nervous system
  - renal
  - hepatic
  - cardiac
  - skin
- Grade 4 haematological toxicities unless any other criteria are met.
- Hospitalisation for chemotherapy administration.
- Expected side effects of chemotherapy (see Section 14 of the SIOP-LGG protocol) unless in the Investigator's opinion they unexpectedly prolonged the hospitalisation or required intensive care therapy.
- Hospitalisation for procedures required by the protocol e.g. biopsy or surgery unless any other criteria are met.
- Hospitalisation due to signs and symptoms of progressive disease unless the outcome is death.
- Elective hospitalisation for a pre-existing condition that has not worsened.
- Disability resulting from tumour surgery.
- Carboplatin allergy unless it manifests as life-threatening allergic shock.

23.2.1 SARs and SUSARs

If the SAE is assessed as having a causal relationship to the IMP, it is classified as a Serious Adverse Reaction (if there is no causal relationship to the IMP e.g. the SAE is related to radiotherapy or surgery etc, then it cannot be a SAR).

If the SAE is deemed to be a Suspected Unexpected Serious Adverse Reaction (SUSAR) because the nature or severity of the event is not consistent with the IMP product information or summary of product characteristics, then the CRCTU will assist the Chief Investigator with the coordination of the expedited reporting to the competent authority and ethics committee and with circulation of the information to each treatment Centre.

If the SUSAR is fatal or life threatening, the CIOMS-1 form must be submitted to the regulatory authority and ethics committee within 7 days of knowledge of the event. Any follow up information should be sent within a further 8 days.

If the SUSAR is not fatal or life threatening, the CIOMS-1 form must be submitted to the regulatory authority and ethics committee within 15 days of knowledge of the event.

APPENDIX 1

CHEMOTHERAPY FLOWCHARTS:

- **STANDARD INDUCTION + CONSOLIDATION- 3 pages**
- **INTENSIVE INDUCTION + CONSOLIDATION- 3 pages**
- **ALTERNATIVE CONSOLIDATION FOLLOWING ALLERGY OR EARLY PROGRESSION- 3 pages**

Name: **DOB:** **Study Number:**	**Protocol: RG_09-201 (SIOP-LGG 2004)** **Regimen: Standard Induction**
Assessment at diagnosis - CT/MRI Scan **Tumour:** **Diagnosis:**	**Ongoing problems:** (Neurology, etc) **Toxicity at diagnosis:** **GFR:** *Corrected=* *mls/min/1.73m²* **Audiology:** **Dose Reduction:** *** For patients < 1 year old or weight < 10kg- refer to protocol for doses**

Week	Date	Treatment	mg/m2*	Given	Drug	mg/m2 *	Given	Complications
1		Vincristine	1.5		Carboplatin	550		
2		Vincristine	1.5					
3		Vincristine	1.5					
4		Vincristine	1.5		Carboplatin	550		
5		Vincristine	1.5					
6		Vincristine	1.5					
7		Vincristine	1.5		Carboplatin	550		
8		Vincristine	1.5					
9		Vincristine	1.5					
10		Vincristine	1.5		Carboplatin	550		
13		Vincristine	1.5		Carboplatin	550		
17		Vincristine	1.5		Carboplatin	550		
21		Vincristine	1.5		Carboplatin	550		
24		**MRI Scan**			**GFR:** *Corrected=* *mls/min/1.73m²*			**Audiology:**

Page 1	**Induction: Weeks 1 - 21** **Consolidation: Weeks 25 – 81**	MRI, GFR and audiology every 6 months on treatment.

Consultant Signature

Name: **DOB:** **Study Number:**	**Protocol: RG_09-201 (SIOP-LGG 2004)** **Regimen: Consolidation**
Assessment Week 24 - Scans **Tumour size:** **Diagnosis:**	**Ongoing problems:** **Toxicity:** **GFR:** *Corrected=* *mls/min/1.73m²* **Dose Reduction:** *** For patients < 1 yr old or weighing < 10kg- refer to protocol for doses**

Week	Date	Treatment	mg/m2*	Given	Drug	mg/m2 *	Given	Complications
25		Vincristine	1.5		Carboplatin	550		
26		Vincristine	1.5					
27		Vincristine	1.5					
31		Vincristine	1.5		Carboplatin	550		
32		Vincristine	1.5					
33		Vincristine	1.5					
37		Vincristine	1.5		Carboplatin	550		
38		Vincristine	1.5					
39		Vincristine	1.5					
43		Vincristine	1.5		Carboplatin	550		
44		Vincristine	1.5					
45		Vincristine	1.5					
49		Vincristine	1.5		Carboplatin	550		
50		Vincristine	1.5					
51		Vincristine	1.5					
54		**MRI Scan**			**GFR:** *Corrected=* *mls/min/1.73m²*			**Audiology:**

Page 2		MRI, GFR & audiology every 6 months on treatment.

Consultant Signature

Name: **DOB:** **Study Number:**	**Protocol: RG_09-201 (SIOP-LGG 2004)** **Regimen: Consolidation (cont.)**
Assessment Week 54 - Scans **Tumour size:** **Diagnosis:**	**Ongoing problems:** **Toxicity:** **GFR:** *Corrected=* *mls/min/1.73m²*
	Dose Reduction: *** For patients < 1 yr old or weighing < 10kg- refer to protocol for doses**

Week	Date	Treatment	mg/m2*	Given	Drug	mg/m2 *	Given	Complications
55		Vincristine	1.5		Carboplatin	550		
56		Vincristine	1.5					
57		Vincristine	1.5					
61		Vincristine	1.5		Carboplatin	550		
62		Vincristine	1.5					
63		Vincristine	1.5					
67		Vincristine	1.5		Carboplatin	550		
68		Vincristine	1.5					
69		Vincristine	1.5					
73		Vincristine	1.5		Carboplatin	550		
74		Vincristine	1.5					
75		Vincristine	1.5					
79		Vincristine	1.5		Carboplatin	550		
80		Vincristine	1.5					
81		Vincristine	1.5					
85		**MRI Scan**			**GFR:** *Corrected=* *mls/min/1.73m²*			**Audiology:**

Page 3	**End of treatment**	MRI, GFR & audiology every 6 months on-treatment

Consultant Signature

CRCTU- RG_09-201 (SIOP-LGG 2004) Intensive Induction + Consolidation v2.0, September 2010

Name: **DOB:** **Study Number:**	**Protocol: RG_09-201 (SIOP LGG-2004)** **Regimen: Intensified Induction**
Assessment at diagnosis - CT/MRI Scan **Tumour:** **Diagnosis:**	**Ongoing problems:** (Neurology, etc) **Toxicity at diagnosis:** **GFR:** *Corrected=* *mls/min/1.73m²* **Audiology:** **Dose Reduction:** ***For patients < 1yr of age or weighing < 10kg- refer to protocol for doses**

Week	Date	Treatment	mg/m2*	Given	Drug	mg/m2*	Given	Drug	mg/m2	Given	Complications
1 (*d1)*		Vincristine	1.5		Carboplatin	550		Etoposide	100		
(d2)								Etoposide	100		
(d3)								Etoposide	100		
2		Vincristine	1.5								
3		Vincristine	1.5								
4 (*d1*)		Vincristine	1.5		Carboplatin	550		Etoposide	100		
(d2)								Etoposide	100		
(d3)								Etoposide	100		
5		Vincristine	1.5								
6		Vincristine	1.5								
7 (*d1*)		Vincristine	1.5		Carboplatin	550		Etoposide	100		
(d2)								Etoposide	100		
(d3)								Etoposide	100		
8		Vincristine	1.5								
9		Vincristine	1.5								
10 (*d1*)		Vincristine	1.5		Carboplatin	550		Etoposide	100		
(d2)								Etoposide	100		
(d3)								Etoposide	100		
13		Vincristine	1.5		Carboplatin	550					
17		Vincristine	1.5		Carboplatin	550					
21		Vincristine	1.5		Carboplatin	550					
24		**MRI Scan**			**GFR:** *Corrected=* *mls/min/1.73m²*						**Audiology:**

Page 1	**Induction: Weeks 1 - 21** **Consolidation: Weeks 25 - 81**	MRI, GFR & audiology every 6 months on treatment.

Consultant Signature

Name: **DOB:** **Study Number:**	**Protocol: RG_09-201 (SIOP LGG-2004)** **Regimen: Consolidation**
Assessment Week 24 - Scans **Tumour size:** **Diagnosis:**	**Ongoing problems:** **Toxicity:** **GFR:** *Corrected=* *mls/min/1.73m²* **Dose Reduction:** *** For patients < 1 yr of age or weighing < 10kg- refer to protocol for doses**

Week	Date	Treatment	mg/m2*	Given	Drug	mg/m2*	Given	Complications
25		Vincristine	1.5		Carboplatin	550		
26		Vincristine	1.5					
27		Vincristine	1.5					
31		Vincristine	1.5		Carboplatin	550		
32		Vincristine	1.5					
33		Vincristine	1.5					
37		Vincristine	1.5		Carboplatin	550		
38		Vincristine	1.5					
39		Vincristine	1.5					
43		Vincristine	1.5		Carboplatin	550		
44		Vincristine	1.5					
45		Vincristine	1.5					
49		Vincristine	1.5		Carboplatin	550		
50		Vincristine	1.5					
51		Vincristine	1.5					
54		**MRI Scan**			**GFR:** *Corrected=* *mls/min/1.73m²*			**Audiology:**

Page 2		MRI, GFR & audiology every 6 months on treatment.

Consultant Signature

Name: **DOB:** **Study Number:**	**Protocol: RG_09-201 (SIOP LGG-2004)** **Regimen: Consolidation (cont.)**
Assessment Week 24 - Scans **Tumour size:** **Diagnosis:**	**Ongoing problems:** **Toxicity:** **GFR:** *Corrected=* *mls/min/1.73m²* **Dose Reduction:** *** For patients < 1yr old or weighing < 10kg- refer to protocol for doses**

Week	Date	Treatment	mg/m2*	Given	Drug	mg/m2*	Given	Complications
55		Vincristine	1.5		Carboplatin	550		
56		Vincristine	1.5					
57		Vincristine	1.5					
61		Vincristine	1.5		Carboplatin	550		
62		Vincristine	1.5					
63		Vincristine	1.5					
67		Vincristine	1.5		Carboplatin	550		
68		Vincristine	1.5					
69		Vincristine	1.5					
73		Vincristine	1.5		Carboplatin	550		
74		Vincristine	1.5					
75		Vincristine	1.5					
79		Vincristine	1.5		Carboplatin	550		
80		Vincristine	1.5					
81		Vincristine	1.5					
85		**MRI Scan**			**GFR:** *Corrected=* *mls/min/1.73m²*			**Audiology:**

Page 3	**End of treatment**	MRI, GFR & audiology every 6 months on treatment.

Consultant Signature

Name: **DOB:** **Study Number:**	**Protocol: RG_09-201 (SIOP-LGG 2004)** **Regimen: Alternative chemotherapy post-allergy or early progression**
Assessment at diagnosis - CT/MRI Scan **Tumour:** **Diagnosis:**	**Ongoing problems:** (Neurology, etc) **Toxicity at diagnosis:** **GFR:** *Corrected=* *mls/min/1.73m²* **Audiology:**
$ cycle length = 6 weeks # Week number when week 1 = date of first induction chemotherapy	**Dose Reduction:** ***For patients < 1 yr or wt < 10kg- refer to protocol for doses**

Cycle (day) $	Date	Week No. #	Treatment	mg/m2 *	Given	Drug	mg/m2 *	Given	Complications
1 (1)			Vincristine	1.5		Cyclophosphamide	1500		
1 (8)			Vincristine	1.5					
1 (15)			Vincristine	1.5					
2 (d1)			Vincristine	1.5		Cisplatin	30		
2 (d2)						Cisplatin	30		
2 (d8)			Vincristine	1.5					
2 (d15)			Vincristine	1.5					
3 (d1)			Vincristine	1.5		Cyclophosphamide	1500		
3 (d8)			Vincristine	1.5					
3 (d15)			Vincristine	1.5					
4 (d1)			Vincristine	1.5		Cisplatin	30		
4 (d2)						Cisplatin	30		
4 (d8)			Vincristine	1.5					
4 (d15)			Vincristine	1.5					
5 (d1)			Vincristine	1.5		Cyclophosphamide	1500		
5 (d8)			Vincristine	1.5					
5 (d15)			Vincristine	1.5					

Page 1	The two combinations shall be given a maximum of 5 times each (i.e. 10 x 6 week chemotherapy cycles in total) however treatment must not continue beyond week 81 from the start of chemotherapy. NB: stop at week 81 or after 10 x 6 week cycles of alternative chemotherapy, whichever comes first	Scans should be performed 24, 54 and 85 weeks after the first date of Induction chemotherapy. GFR & audiology every 6 months as a minimum.

Consultant Signature

Name: **DOB:** **Study Number:**	**Protocol: RG_09-201 (SIOP-LGG 2004)** **Regimen: Alternative consolidation post-allergy or early progression (cont.)**
Assessment Week 24 or 54 - Scans **Tumour size:** **Diagnosis:**	**Ongoing problems:** **Toxicity:** **GFR:** *Corrected=* *mls/min/1.73m²* **Audiology:**
$ cycle length = 6 weeks # Week number when week 1 = date of first induction chemotherapy	**Dose Reduction:** ***For patients < 1 yr old or weighing < 10kg- refer to protocol for doses**

Cycle (day) $	Date	Week No. #	Treatment	mg/m2 *	Given	Drug	mg/m2 *	Given	Complications
6 (d1)			Vincristine	1.5		Cisplatin	30		
6 (d2)						Cisplatin	30		
6 (d8)			Vincristine	1.5					
6 (d15)			Vincristine	1.5					
7 (d1)			Vincristine	1.5		Cyclophosphamide	1500		
7 (d8)			Vincristine	1.5					
7 (d15)			Vincristine	1.5					
8 (d1)			Vincristine	1.5		Cisplatin	30		
8 (d2)						Cisplatin	30		
8 (d8)			Vincristine	1.5					
8 (d15)			Vincristine	1.5					
9 (d1)			Vincristine	1.5		Cyclophosphamide	1500		
9 (d8)			Vincristine	1.5					
9 (d15)			Vincristine	1.5					

Page 2	The two combinations shall be given a maximum of 5 times each (i.e. 10 x 6 week chemotherapy cycles in total) however treatment must not continue beyond week 81 from the start of chemotherapy. NB: stop at week 81 or after 10 x 6 week cycles of alternative chemotherapy, whichever comes first	Scans should be performed 24, 54 and 85 weeks after the first date of Induction chemotherapy. GFR & audiology every 6 months as a minimum.

Consultant Signature

Name: **DOB:** **Study Number:**	**Protocol: RG_09-201 (SIOP-LGG 2004)** **Regimen: Alternative Consolidation post-allergy or early progression (cont.)**
Assessment Week 24 or 54- Scans **Tumour size:** **Diagnosis:**	**Ongoing problems:** **Toxicity:** **GFR:** *Corrected=* *mls/min/1.73m²* **Audiology:**
$ cycle length = 6 weeks # Week number when week 1 = date of first induction chemotherapy	**Dose Reduction:** ***For patients < 1 yr old or weight < 10kg- refer to protocol for doses**

Cycle (day) $	Date	Week No. #	Treatment	mg/m2*	Given	Drug	mg/m2 *	Given	Complications
10 (d1)			Vincristine	1.5		Cisplatin	30		
10 (d2)						Cisplatin	30		
10 (d8)			Vincristine	1.5					
10(d15)			Vincristine	1.5					
			MRI Scan						

Page 3	**End of treatment** The two combinations shall be given a maximum of 5 times each (i.e. 10 x 6 week chemotherapy cycles in total) however treatment must not continue beyond week 81 from the start of chemotherapy. NB: stop at week 81 or after 10 x 6 week cycles of alternative chemotherapy, whichever comes first	Scans should be performed 24, 54 and 85 weeks after the first date of Induction chemotherapy. GFR & audiology every 6 months as a minimum.

Consultant Signature

APPENDIX 2

Overview of Parent/Patient Information Sheets

1 Hypothalamic chiasmatic visual pathway tumours: observation study

Information Sheet for parents/guardians and patients aged 13+ years
Information Sheet for younger children
Parent/child consent form
Consent form for patients aged 16+ years
Information Sheet for GP

2 Children with Neurofibromatosis type-1

Information Sheet for parents/guardians and patients aged 13+ years
Information Sheet for younger children
Parent/child consent form
Consent form for patients aged 16+ years
Information Sheet for GP

3 Randomised comparison of two drugs versus three drugs in induction chemotherapy

Parent/Guardian Information Sheet
Information Sheet for 13-15 year olds
Information Sheet for 8-12 year olds
Information Sheet to be read to children under 8 years old
Parent/child consent form
Information Sheet for GP

4 Observational Study- Non-hypothalamic chiasmatic visual pathway tumours

Information Sheet for parents/guardians and patients aged 13+ years
Information Sheet for younger children
Parent/child consent form
Consent form for patients aged 16+ years
Information Sheet for GP

5 Radiotherapy Treatment Study

Parent/Guardian Information Sheet
Information Sheet for patients aged 16+ years
Information Sheet for children aged 13-15 years
Information Sheet for 8-12 year olds
Information Sheet to be read to children under 8 years old
Parent/child consent form
Consent form for patients aged 16+ years
Information Sheet for GP

6 Non Randomised Chemotherapy Treatment

Information Sheet for parents/guardians and patients aged 13+ years

Information Sheet for younger patients

Parent/child consent form

Consent form for patients aged 16+ years

Information Sheet for GP