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[Intervention Protocol]

Focal laser treatment in addition to chemotherapy for retinoblastoma

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ABSTRACT

This is the protocol for a review and there is no abstract. The objectives are as follows:

To compare the effectiveness and safety of adding focal laser therapy to systemically-delivered chemotherapy in treating intraocular retinoblastoma.

BACKGROUND

Description of the condition

Retinoblastoma is the most common intraocular malignancy of childhood, with a constant incidence worldwide of 1:15,000 to 1:20,000 livebirths (Kivela 2009). In most cases the tumour is initiated by a mutation in the *RB1* gene, a tumour suppressor gene located on chromosome 13q14, and mutations in both *RB1* alleles are a prerequisite for developing the cancer (Knudson 1971). In heritable retinoblastoma, in which in most cases both eyes are clinically affected, mutation in one *RB1* allele is constitutional, whereas a somatic mutation in the second allele initiates tumour growth in the sensory retinal cells. In non-heritable *RB1*-related retinoblastoma, both mutations are somatic, which gives rise to unilateral disease in most cases. Retinoblastoma patients with the heritable form are also prone to developing additional non-ocular tumours (Eng 1993), and are at higher risk of developing trilateral retinoblastoma, i.e. ocular retinoblastoma in conjunction with an

intracranial midline primitive neuroectodermal tumour (de Jong 2015).

The median age of diagnosis of unilateral retinoblastoma is 24 months and of bilateral retinoblastoma is 10 months (MacCarthy 2009). A white pupillary reflex, also termed leukocoria, is the most common presenting clinical sign in both developing and developed countries (Abramson 1998; Bowman 2008; Menon 2009). Additional signs are strabismus, usually when the macula is involved, and less frequently red eye, inflammation and additional non-specific signs (Abramson 1998). Early detection and urgent referral to specialised retinoblastoma centres is of utmost importance in order to salvage life, eye and vision. If untreated, retinoblastoma will spread outside the globe, via the central nervous system, and haematogenously, inevitably leading to death. In developing countries, in which there is a lack of educational strategies and infrastructure is poor, retinoblastoma patients' survival rate is estimated to be 40% or less (Dimaras 2012; Kivela 2009). In developed countries, while these were the survival rates in early 20th century, currently the five-year survival is estimated to be over 95% (Shields 2004).

Treatment strategies for retinoblastoma have evolved significantly throughout the years. Traditionally, retinoblastoma was treated by removal of the eyeball (i.e. enucleation), a definite cure when the tumour is contained within the globe. In advanced cases with extraocular tumour extension, enucleation alone is not curative, and further treatment is warranted. Currently, enucleation is reserved only for advanced stage intraocular disease or as salvage treatment after failure of other conservative modalities.

In seeking a treatment modality with better outcomes and less morbidity, external beam radiotherapy (EBRT) was found to be an effective alternative, and by the mid-20th century had largely replaced enucleation as the mainstay treatment for most retinoblastoma cases (Reese 1949; Stallard 1952). In order to better predict outcomes of retinoblastoma patients treated with EBRT, the Reese-Ellsworth (R-E) classification for intraocular retinoblastoma was developed (Reese 1964). It soon became an essential tool in its management, and also enabled comparison of study results from different centres. Unfortunately, after nearly half a century of extensive use of EBRT for retinoblastoma, it was recognised that radiation significantly increases the risk to developing a secondary cancer in survivors of hereditary retinoblastoma (Fletcher 2004; Kleinerman 2005). As a result, radiotherapy was widely abandoned and replaced by chemotherapy as the primary treatment for intraocular retinoblastoma. To date, it is reserved only as a last resort when all other modalities have failed.

Description of the intervention

Systemically administered chemotherapy for retinoblastoma is used as adjuvant treatment when high-risk histopathological features are found after enucleation, to treat systemic retinoblastoma spread and as primary treatment for intraocular disease. Kupfer 1953 described the first use of chemotherapy for the latter indication and attempts to combine EBRT and chemotherapy were soon published (Reese 1958). However, it was abandoned and for many years reserved only for extraocular disease. The use of systemic chemotherapy as a primary treatment modality for intraocular disease was revived in the 1990s in London using potent chemotherapeutic agents, namely vincristine, etoposide and carboplatin (VEC). The VEC regimen was first given in combination with EBRT and resulted in 70% of eyes salvaged (Kingston 1996). In subsequent studies, systemic chemotherapy with additional focal therapy was used as an alternative to EBRT and resulted with high eye salvage rate (Gallie 1996; Murphree 1996; Shields 1996). Soon after it was first introduced, the VEC regimen became the standard protocol, given through a central venous access line every three weeks for six cycles. In order to better predict the outcomes of retinoblastoma patients treated with chemotherapy, a new classification scheme, the International Classification of Retinoblastoma (ICRB), was introduced in early 2000s to replace the R-E classification, which became less relevant (Murphree 2005). One of the main features integrated into the ICRB scheme was the presence of retinoblas-

toma seeds (vitreous or subretinal, or both), as it was recognised that seeding is a predictor for failure after chemotherapy. Despite some discrepancies in its interpretation, the ICRB is currently used throughout the world (Novetsky 2009). Early use of systemic chemotherapy in conjunction with radiation was reported to cause serious side effects and therefore abandoned (Reese 1958). In the VEC regimen era, possible chemotherapy-related side effects include febrile episodes, temporary alopecia, bone marrow suppression, peripheral neuropathy and allergic reactions to the substances used, but the incidences of which are poorly documented. Carboplatin was suggested to cause ototoxicity (Lambert 2008), and etoposide to induce secondary acute myelogenous leukaemia (Gombos 2007; Turaka 2012); both on rare occasions. In an attempt to avoid potential systemic complications of systemically-delivered chemotherapy, new methods of delivery were developed, namely intra-arterial and intravitreal chemotherapy. The former method of delivery was developed in Japan (Yamane 2004), and was refined in the USA (Abramson 2008). The latter was developed in Sweden (Ericson 1961; Seregard 1995), and is extensively used in Japan and Switzerland (Kaneko 2003; Munier 2012). There is increasing enthusiasm towards the use of these selective modalities, and in some centres they have replaced systemic chemotherapy as a primary treatment for intraocular retinoblastoma (Abramson 2015). Despite these trends, the indications for use and whole spectrum of side effects and complications are not yet fully understood. Worldwide, systemically-delivered chemotherapy remains a major therapeutic option for unilateral and especially bilateral retinoblastoma.

Focal laser is the treatment of choice for small postequatorial tumours. It is also used in combination or after administration of chemotherapy for larger tumours and for tumour recurrence (retinal or subretinal) after successful initial treatment by various modalities. Though it was initially performed by means of light photocoagulation, currently most centres use an 810 nm modified diode laser, termed transpupillary thermotherapy (TTT). Legendijk 1982 performed the first description of TTT as treatment for intraocular retinoblastoma, which used a microwave applicator and successfully treated two patients with recurrent disease. It has since been used successfully as a primary sole treatment for ICRB group A eyes, and has resulted in a high rate of tumour control. Shields 1999 used TTT to primarily treat 188 tumours in a mean base diameter of 3 mm and elevation of 2 mm, and showed that a complete regression was achieved in 86% of the tumours. In a case series of 91 tumours that measured less than 1.5 disc diameters (DD), Abramson 2004a showed that 92% of the tumours were cured with TTT alone. The procedure is performed using indirect ophthalmoscopy through dilated pupils, with the laser beam exiting the head piece and aimed at the intraocular tumour. The laser is applied for a prolonged period of time (minimum nine seconds per application) as compared to laser photocoagulation. The number of applications, spot size, power energy and treatment end points vary between different centres (Abramson 2004a;

Brichard 2002; Levy 1998; Lumbroso 2002; Shields 2002).

How the intervention might work

Systemic chemotherapy

Historically, chemotherapy was considered to be ineffective for intraocular retinoblastoma, and therefore was not used for this indication (White 1983). However, several advances in the field of chemotherapy for paediatric cancers have driven physicians and scientists to revisit this paradigm: carboplatin, a cisplatin analogue with an improved side effect profile, was found to be an effective chemotherapeutic agent for other neuroectodermal solid tumours (i.e. neuroblastoma) (Gaynon 1994), was shown to cross the blood-brain barrier (Riccardi 1992), and together with etoposide was found to be effective for extraocular retinoblastoma (Doz 1995). Kingston and colleagues' above-mentioned pilot study using VEC in conjunction to EBRT, salvaging most R-E group V eyes (Kingston 1996), paved the way for additional clinical trials and also empirical experimental studies. Murphree and colleagues measured carboplatin concentrations in enucleated retinoblastoma eyes after systemic administration of the agent and found it was at significant levels (Murphree 1996). In addition, carboplatin was found to effectively inhibit tumour growth in both in vivo and in vitro experimental models (Harbour 1996; Murray 1997).

Systemic chemotherapy and focal laser treatment

While some use chemotherapy as the sole primary treatment for intraocular retinoblastoma (Gombos 2002), others claim it to be insufficient to combat the disease; they have stated that it merely reduces tumour size, thus enabling further focal therapies to be applied to achieve full tumour control (Murphree 1996; Shields 1996; Shields 2005). The use of chemotherapy in this manner, termed chemoreduction, has roots in treatments of other solid tumours (Dropcho 1992; Follézou 1989; Lerner 1995). In a study by Shields and colleagues, chemotherapy for intraocular retinoblastoma resulted in complete tumour response in 46% of the patients and a partial response that warranted additional focal treatments in the remaining patients (Shields 1996). None of the patients required enucleation, although EBRT was necessary in 29% of eyes because of diffuse vitreous seeds. Wilson 2001 treated 20 retinoblastoma patients with eight cycles of vincristine and carboplatin, and found that in 92% of cases tumours progressed after chemotherapy and required adjuvant supplemental focal therapies. Shields 2005 performed a prospective non-randomised study in which 28 of 68 tumours were treated by means of systemic chemotherapy alone and 40 of 68 were treated with chemotherapy combined with foveal-sparing TTT. The study findings indicated that recurrence in the group that received chemotherapy alone

occurred in 35% of tumours at four years follow-up versus 17% in the combined treatment group. In support of the combined use of TTT and chemotherapy, not only the insufficient role of chemotherapy alone is stated but also the beneficial interaction of heat energy and chemotherapy. The use of thermal energy in conjunction with chemotherapy has been shown to be synergistic (Da Silva 1987; Herman 1994), and to enhance the cytotoxic effect of carboplatin in vivo (Tapazoglou 1991). In addition, in a transgenic murine retinoblastoma cell line, the cytotoxic interaction of heat and carboplatin were found to be superior to each of the monotherapies (Murray 1997). Lumbroso 2002 treated 51 children (103 tumours) with TTT that was administered shortly after injection of carboplatin. Over 96% of tumours regressed after a median follow-up time of 30 months. The use of systemic chemotherapy alone for intraocular retinoblastoma was advocated as focal laser therapy was found to cause large scotomas (Abramson 2004b). The laser scar may also increase in size (Lee 2004). Also, rates of vitreous or vitreous base relapse are thought to increase with a longer duration of TTT (Gombos 2006). Scheffler and colleagues assessed patients treated with chemotherapy and repetitive TTT ablations (Scheffler 2007). Nearly 90% of eyes achieved control at three years follow-up. However, over 60% of children developed iris atrophy with laser treatment. Gombos and colleagues retrospectively reviewed retinoblastoma patients treated with primary systemic chemotherapy alone and found that in 72% of cases there was no need for additional treatment (Gombos 2002).

Why it is important to do this review

To date there has been no systematic review of randomised trials to summarise the evidence of the effectiveness and safety of focal laser therapy in retinoblastoma patients treated with systemic chemotherapy. Also, there is no consensus as to the preferred timing of laser therapy application, if used, after chemotherapy administration. While in some practices focal laser treatment is added only if required, in others it is used at a prefixed timing in regard to the chemotherapy courses given (i.e. before or after a specific predetermined chemotherapy course). In addition, there is clinical uncertainty as for which group classification (R-E or ICRB) focal laser treatment is best used as an adjunct to systemic chemotherapy.

As retinoblastoma is a sight- and life-threatening disease, it is important to establish the preferred practice in terms of efficacy and safety of focal laser therapy added to systemically-delivered chemotherapy.

OBJECTIVES

To compare the effectiveness and safety of adding focal laser therapy to systemically-delivered chemotherapy in treating intraocular retinoblastoma.

METHODS

Criteria for considering studies for this review

Types of studies

We will only include randomised controlled trials (RCTs).

Types of participants

Participants diagnosed with intraocular postequatorial retinoblastoma in either one or both eyes. There will be no restrictions regarding age, gender, ethnicity, co-morbidities of participants or the number of trial participants.

Types of interventions

We will include trials that compare chemotherapy plus laser treatment versus chemotherapy alone. There will be no restrictions on the type of laser used (i.e. laser beam wavelength).

Types of outcome measures

Primary outcomes

The proportion of eyes with recurrence of tumours within three years from treatment.

Secondary outcomes

- The proportion of eyes that require external beam radiotherapy (EBRT) or enucleation at any time point.
- The proportion of enucleated eyes at any time point with high risk histopathological characteristics for tumour progression and metastasis (i.e. invasion of the postlaminar optic nerve, choroid, sclera and anterior chamber) (Khelifaoui 1996).
- The proportion of enucleated eyes with extraocular tumour spread at any time point.
- Metastatic spread: the proportion of participants with distant metastatic spread at any time point.
- Survival: the proportion of participants that died due to metastatic spread at any time point.
- Total number of additional treatments given.
- Time from last treatment (i.e. chemotherapy or laser treatment) to tumour relapse.
- Visual acuity of 6/60 or better versus worse than 6/60 measured at least 12 months after initial treatment.

Adverse outcomes

We will compare complications and adverse events between treatment groups that occur throughout follow-up for all included trials. Complications will include those from chemotherapy or use of laser therapy, or both. Adverse effects of interest will include but will not be limited to the following.

- Retinal scar.
- Retinal tear.
- Development of vitreous seeds.
- Iris atrophy.
- Neovascularisation at the disc, retina elsewhere, iris or anterior chamber angle.
- Chorio-retinal ischaemia.
- Systemic adverse effects of any kind.
- Death.

Follow-up

We will not place any restrictions on the duration of follow-up.

Search methods for identification of studies

Electronic searches

We will search CENTRAL (which contains the Cochrane Eyes and Vision Trials Register) (latest issue), Ovid MEDLINE, Ovid MEDLINE In-Process and Other Non-Indexed Citations, Ovid MEDLINE Daily, Ovid OLDMEDLINE (January 1946 to present), Embase (January 1980 to present), Latin American and Caribbean Health Sciences Literature Database (LILACS) (1982 to present), the ISRCTN registry (www.isrctn.com/editAdvancedSearch), ClinicalTrials.gov (www.clinicaltrials.gov) and the World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP) (www.who.int/ictcp/search/en). We will not use any date or language restrictions in the electronic search for trials.

See: Appendices for details of search strategies for CENTRAL (Appendix 1), MEDLINE (Appendix 2), Embase (Appendix 3), LILACS (Appendix 4), ISRCTN (Appendix 5), ClinicalTrials.gov (Appendix 6) and the WHO ICTRP (Appendix 7).

Searching other resources

We will search the citation lists of reports from trials we identify from the literature search to look for additional trials. We will not conduct manual searches of conference proceedings or abstracts specifically for this review.

Data collection and analysis

Selection of studies

Two review authors will independently screen the titles and abstracts that result from the searches by using internet-based software (Covidence 2015). They will classify each record as either 'definitely relevant', 'possibly relevant' or 'irrelevant'. They will obtain full-text copies of records classified as 'definitely relevant' or 'possibly relevant' after discussion between the review authors. They will classify each full-text report as either 'included', 'awaiting assessment' or 'excluded'. A third review author will resolve any disagreements regarding full-text assessments. For studies written in languages not understood by the review authors, we will use Google Translate or we will request translation of the full-text report in order to determine eligibility. We will contact the primary study investigators to clarify the eligibility of studies classified as 'awaiting assessment'. We will document the reasons for excluding studies identified by both review authors as 'excluded'. Also, we will list the excluded studies and their reasons for exclusion in a 'Characteristics of excluded studies' table. The review authors will not be masked to the report authors, institutions and trial results during these assessments. We will create a PRISMA diagram to illustrate the study selection process.

Data extraction and management

Two review authors will independently extract data using a prepiloted online form and the web-based software Covidence (Covidence 2015). One review author will enter data into Review Manager (RevMan) (RevMan 2014), and the second review author will review the accuracy of the work performed by the first review author.

Assessment of risk of bias in included studies

Two review authors will assess the risk of bias in the included studies using the Cochrane 'Risk of bias' assessment tool as described in Chapter 8 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). This assessment will include assessing sequence generation, allocation concealment, completeness of data, selective outcome reporting and other potential sources of bias. We will construct a 'Risk of bias' table, in which we will identify whether any of these types of bias are present in each included study, the risk that the bias compromised the results of the study and supporting evidence for these judgments. Two review authors will conduct these assessments and will resolve any disagreements by consensus or arbitration by a third review author.

Measures of treatment effect

We will present dichotomous data as risk ratios with 95% confidence intervals (CIs).

- Primary outcome: proportion of eyes with recurrence of tumours within three years from treatment.
- Secondary outcome: proportion of eyes (enucleated or treated with EBRT, eyes with high risk histopathological features and eyes with extraocular tumour spread), proportion of participants (distant metastatic spread and death), visual acuity (better versus worse than 6/60).
- Adverse outcomes.

We will present continuous data as mean differences with 95% CIs.

- Secondary outcome: number of additional treatments, visual acuity and visual field when assessed as means or mean deviation.

Unit of analysis issues

In our analyses, we will compare eyes treated with chemotherapy and additional laser therapy versus those treated with chemotherapy alone. Trials may randomise tumours, eyes or participants to the intervention or comparator. We will record details of study design with respect to treatment modality (chemotherapy with/without laser therapy), treatment of one or more tumours, one or both eyes of the participant. If a study randomly allocates participants to treatment but includes and reports all tumours or both eyes, we will analyse the data as 'clustered data', i.e. we will adjust for within-person correlation. If insufficient information is available in the article, we will attempt to contact the study authors for clarification.

Dealing with missing data

We anticipate that missing data will be present within the included studies. We will analyse studies using an available-case analysis. We will record the percentage of missing data from each intervention group in all included studies, and examine the reasons, to determine whether it meets the assumption of data being missing at random. We will consider studies that exhibit an unequal rate (greater than 20%) of missing data between intervention groups as at risk of attrition bias.

Assessment of heterogeneity

We will assess heterogeneity and inconsistency among trials statistically using the I^2 statistic value to assess if variability in effect is due to sampling error. We will also assess diversity between the included studies by reviewing participant characteristics and trial methodology.

Assessment of reporting biases

We will assess selective outcome reporting when we judge individual studies for risk of bias. We will assess reporting biases by examining funnel plots when we include 10 or more RCTs in meta-analyses.

Data synthesis

When we do not detect any substantial clinical or methodological heterogeneity, we will combine the results in a meta-analysis. If there are three or fewer eligible RCTs, then we will use a fixed-effect model for the meta-analysis. If more than three trials meet the inclusion criteria, we will use a random-effects model. If substantial heterogeneity is present and the direction of effect is inconsistent across the included studies, we will not combine the data in a meta-analysis but we will present a descriptive summary.

Subgroup analysis and investigation of heterogeneity

We will attempt to perform a subgroup analysis according to tumour grouping (i.e. Reese-Elsworth Classification I-V (R-E I-V) and International Classification of Retinoblastoma groups A-E (ICRB A-E)).

Sensitivity analysis

We will conduct one sensitivity analysis, and will exclude studies that are at high risk of bias in one or more domain.

'Summary of findings' table

Two review authors will independently assess the overall quality of the evidence for each outcome using the GRADE classification (GRADEpro 2014). We will include the following outcomes in the 'Summary of findings' table.

- The proportion of eyes with recurrence of tumours within three years from treatment.
- The proportion of eyes that require EBRT or enucleation at any time point.
- The proportion of enucleated eyes at any time point with high risk histopathological characteristics for tumour progression and metastasis.
- The proportion of enucleated eyes with extraocular tumour spread at any time point.
- The proportion of participants with distant metastatic spread at any time point.
- The proportion of participants that died due to metastatic spread at any time point.
- Adverse outcomes.

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- * Indicates the major publication for the study

APPENDICES

Appendix I. CENTRAL search strategy

- #1 MeSH descriptor: [Retinal Neoplasms] explode all trees
 #2 retinoblastoma*
 #3 retina* near/3 (cancer* or neoplas* or tumor* or tumour* or malignan* or carcinoma* or adenocarcinoma* or sarcoma*)
 #4 MeSH descriptor: [Eye Enucleation] explode all trees
 #5 enucleat* or enicerat*
 #6 (eye* or globe) near/2 (remov* or extract*)
 #7 #1 or #2 or #3 or #4 or #5 or #6
 #8 MeSH descriptor: [Antineoplastic Agents] explode all trees
 #9 MeSH descriptor: [Antineoplastic Combined Chemotherapy Protocols] this term only
 #10 MeSH descriptor: [Combined Modality Therapy] explode all trees

- #11 chemotherap* or chemoreduct* or chemothermotherap* or chemoprophyla*
- #12 MeSH descriptor: [Vincristine] this term only
- #13 MeSH descriptor: [Etoposide] this term only
- #14 MeSH descriptor: [Carboplatin] this term only
- #15 vincristine* or etoposide* or carboplatin*
- #16 #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15
- #17 MeSH descriptor: [Lasers] explode all trees
- #18 MeSH descriptor: [Light Coagulation] this term only
- #19 laser*
- #20 photocoagulat*
- #21 transpupillary near/2 thermotherap*
- #22 TTT
- #23 #17 or #18 or #19 or #20 or #21 or #22
- #24 #7 and #16 and #23

Appendix 2. MEDLINE (Ovid) search strategy

1. randomized controlled trial.pt.
2. (randomized or randomised).ab,ti.
3. placebo.ab,ti.
4. dt.fs.
5. randomly.ab,ti.
6. trial.ab,ti.
7. groups.ab,ti.
8. or/1-7
9. exp animals/
10. exp humans/
11. 9 not (9 and 10)
12. 8 not 11
13. exp Retinal Neoplasms/
14. retinoblastoma\$.tw.
15. (retina\$ adj3 (cancer\$ or neoplas\$ or tumor\$ or tumour\$ or malignan\$ or carcinoma\$ or adenocarcinoma\$ or sarcoma\$)).tw.
16. Eye Enucleation/
17. (enucleat\$ or envicerat\$).tw.
18. ((eye\$ or globe) adj2 (remov\$ or extract\$)).tw.
19. or/13-18
20. exp Antineoplastic Agents/
21. Antineoplastic Combined Chemotherapy Protocols/
22. exp Combined Modality Therapy/
23. (chemotherap\$ or chemoreduct\$ or chemothermotherap\$ or chemoprophyla\$).tw.
24. Vincristine/
25. Etoposide/
26. Carboplatin/
27. (vincristine\$ or etoposide\$ or carboplatin\$).tw.
28. or/20-27
29. exp Lasers/
30. Light Coagulation/
31. laser\$.tw.
32. photocoagulat\$.tw.
33. (transpupillary adj2 thermotherap\$).tw.
34. TTT.tw.
35. or/29-34

36. 12 and 19 and 28 and 35

The search filter for trials at the beginning of the MEDLINE strategy is from the published paper by Glanville [Glanville 2006](#).

Appendix 3. Embase (Ovid) search strategy

1. exp randomized controlled trial/
2. exp randomization/
3. exp double blind procedure/
4. exp single blind procedure/
5. random\$.tw.
6. or/1-5
7. (animal or animal experiment).sh.
8. human.sh.
9. 7 and 8
10. 7 not 9
11. 6 not 10
12. exp clinical trial/
13. (clin\$ adj3 trial\$).tw.
14. ((singl\$ or doubl\$ or trebl\$ or tripl\$) adj3 (blind\$ or mask\$)).tw.
15. exp placebo/
16. placebo\$.tw.
17. random\$.tw.
18. exp experimental design/
19. exp crossover procedure/
20. exp control group/
21. exp latin square design/
22. or/12-21
23. 22 not 10
24. 23 not 11
25. exp comparative study/
26. exp evaluation/
27. exp prospective study/
28. (control\$ or prospectiv\$ or volunteer\$).tw.
29. or/25-28
30. 29 not 10
31. 30 not (11 or 23)
32. 11 or 24 or 31
33. exp eye tumor/
34. retinoblastoma\$.tw.
35. (retina\$ adj3 (cancer\$ or neoplas\$ or tumor\$ or tumour\$ or malignan\$ or carcinoma\$ or adenocarcinoma\$ or sarcoma\$)).tw.
36. Eucleation/
37. (enucleat\$ or envicerat\$).tw.
38. ((eye\$ or globe) adj2 (remov\$ or extract\$)).tw.
39. or/33-38
40. exp chemotherapy/
41. antineoplastic agent/
42. multimodality cancer therapy/
43. chemoprophylaxis/
44. (chemotherap\$ or chemoreduct\$ or chemothermotherap\$ or chemoprophyla\$).tw.
45. vincristine/
46. etoposide/
47. carboplatin/

48. (vincristine\$ or etoposide\$ or carboplatin\$.tw.
 49. or/40-48
 50. exp laser/
 51. exp laser coagulation/
 52. laser\$.tw.
 53. photocoagulat\$.tw.
 54. (transpupillary adj2 thermotherap\$).tw.
 55. TTT.tw.
 56. or/50-55
 57. 39 and 49 and 56
 58. 32 and 57

Appendix 4. LILACS search strategy

retinoblastoma or enucleat\$ or eviserat\$ or retinal cancer\$ or retinal neoplasm\$ or retinal tumor\$ or retinal tumour\$ or retinal malignan\$ or retinal carcinoma\$ or retinal adenocarcinoma\$ or retinal sarcoma and chemotherapy or antineoplastic or chemoreduction or chemothermotherapy or chemoprophylaxis or vincristine or etoposide or carboplatin and laser\$ or photocoagulat\$ or coagulat\$ or thermotherap\$

Appendix 5. ISRCTN search strategy

(retinoblastoma OR enucleation OR eviserate OR retinal cancer OR retinal neoplasm OR retinal tumor OR retinal tumour OR retinal malignant OR retinal carcinoma OR retinal adenocarcinoma OR retinal sarcoma) AND (chemotherapy OR antineoplastic OR chemoreduction OR chemothermotherapy OR chemoprophylaxis OR vincristine OR etoposide OR carboplatin)

Appendix 6. ClinicalTrials.gov search strategy

(retinoblastoma OR enucleation OR eviserate OR retinal cancer OR retinal neoplasm OR retinal tumor OR retinal tumour OR retinal malignant OR retinal carcinoma OR retinal adenocarcinoma OR retinal sarcoma) AND (chemotherapy OR antineoplastic OR chemoreduction OR chemothermotherapy OR chemoprophylaxis OR vincristine OR etoposide OR carboplatin)

Appendix 7. WHO ICTRP search strategy

(retinoblastoma OR enucleation OR eviserate OR retinal cancer OR retinal neoplasm OR retinal tumor OR retinal tumour OR retinal malignant OR retinal carcinoma OR retinal adenocarcinoma OR retinal sarcoma) = CONDITION AND (chemotherapy OR antineoplastic OR chemoreduction OR chemothermotherapy OR chemoprophylaxis OR vincristine OR etoposide OR carboplatin) = INTERVENTION

Appendix 8. Data on study characteristics

Mandatory items	Optional items
Methods	
Study design	<ul style="list-style-type: none"> Parallel group RCT i.e. people randomised to treatment. Exclusions after randomisation Losses to follow-up

(Continued)

	<ul style="list-style-type: none"> • Within-person RCT i.e. eyes randomised to treatment. • Cluster RCT i.e. communities randomised to treatment. • Cross-over RCT. • Other, specify. 	Number randomised/analysed How were missing data handled? e.g. available-case analysis, imputation methods Reported power calculation (Y/N), if yes, sample size and power Unusual study design/issues
Eyes or unit of randomisation/unit of analysis	<ul style="list-style-type: none"> • One eye included in the study; specify how the eye was selected. • Two eyes included in the study, both eyes received same treatment; briefly specify how analysed (best/worst/average/both and adjusted for within person correlation/both and not adjusted for within person correlation) and specify if a mixture of 1 eye and 2 eyes. • Two eyes included in study, eyes received different treatments, specify if correct pair-matched analysis was done. 	
Participants		
Total number of participants	This information should be collected for total study population recruited into the study. If the study only reports these data for the participants who were followed up only, please indicate	Setting Ethnic group
Number (%) of men and women		
Average age and age range		
Inclusion criteria		
Exclusion criteria		
Interventions		
Intervention (N =) Comparator (N =) (See MECIR 65 and 70)	<ul style="list-style-type: none"> • Number of people randomised to this group. • Drug (or intervention) name. • Dose. • Frequency. • Route of administration. 	
Outcomes		
Primary and secondary outcomes as defined in study reports (See MECIR R70)	List outcomes Adverse events reported (Y/N) Length of follow-up and intervals at which outcomes assessed	Planned/actual length of follow-up

(Continued)

Notes		
Date conducted	Specify dates of recruitment of participants month/year (mm/yr) to mm/yr	Full study name: (if applicable) Reported subgroup analyses (Y/N) Were trial investigators contacted?
Sources of funding		
Declarations of interest (See MECIR 69)		
<i>Abbreviations</i> MECIR: Methodological Expectations of Cochrane Intervention Reviews; RCT: randomised controlled trial		

CONTRIBUTIONS OF AUTHORS

IDF did a literature search and wrote the first protocol draft. All co-authors performed a literature search, examined the protocol and provided intellectual input. AWS assessed the [Methods](#) section and provided comments. MAR edited the draft significantly.

DECLARATIONS OF INTEREST

IDF: none known.

KPJ: none known.

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