

# BMJ Open The International Vitreoretinal B-Cell Lymphoma Registry: a protocol paper

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## ABSTRACT

**Introduction** Vitreoretinal lymphoma is a rare ocular cancer with high morbidity and mortality despite treatment. Diagnosis by cytopathology is often delayed, and various molecular and image-based investigations have been developed. Diverse treatments are used, but there is a limited medical evidence to differentiate their effectiveness. We designed an international registry that would collect diagnostic, treatment and outcomes data, to establish new evidence for the management of this cancer.

**Methods and analysis** The International Vitreoretinal B-Cell Lymphoma Registry will accrue data retrospectively for individuals aged 18 years or older, diagnosed with new or recurrent vitreoretinal B-cell lymphoma on or after 1 January 2020. A steering committee of subspecialised ophthalmologists identified 20 key clinical data items that describe patient demographics, tissue involvements, diagnostic testing, ocular and systemic treatments and treatment complications, and visual acuity and survival outcomes. Customised software was designed to permit collection of these data across a single baseline and multiple follow-up forms. The platform collects data without identifiers and at 3 month reporting intervals. Outcomes of the project will include: (1) descriptions of clinical presentations, and diagnostic and therapeutic preferences; (2) associations between clinical presentations, and diagnostics and treatments, and between diagnostics and treatments (assessed by ORs with 95% CIs); and (3) estimations of rates of vision loss, and progression-free and overall survival (assessed by Kaplan-Meier estimates).

**Ethics and dissemination** The registry has received Australia-wide approval by a national human research ethics committee. Sites located outside Australia are required to seek local human research ethics review. Results generated through the registry will be disseminated primarily by peer-reviewed publications that are expected to inform clinical practice, as well as educational materials.

## INTRODUCTION

Vitreoretinal lymphoma is an ocular cancer that has both high morbidity and high mortality.<sup>1</sup> In the majority of cases, the cancer is a diffuse large B-cell non-Hodgkin lymphoma based in vitreous, retina and/or optic nerve; although other subtypes of

## STRENGTHS AND LIMITATIONS OF THIS STUDY

- ⇒ We describe an international clinical registry that will collect real-world data related to the course, management and outcomes of vitreoretinal lymphoma, tracking right and left eyes separately.
- ⇒ Data are collected without personal identifiers, and a key design feature is the use of 3 monthly reporting intervals, since specific dates may provide clues to individual identities.
- ⇒ Limitations of any registry include selection bias, and errors and omissions during data entry. However, conditional fields and manual cross-referencing across entries have been implemented for high-quality data.
- ⇒ Information to be collected initially is limited to common diagnostic tests and treatments, but this was done to encourage involvement and compliance, and data collection can be expanded as the project gains momentum.

B-cell and T-cell lymphoma are described, these are exceptional.<sup>2</sup> Patients with vitreoretinal lymphoma experience a range of visual symptoms, and floaters and blurred vision are common complaints. In the typical case, examination of the eyes reveals bilateral involvement, with veils and strings of lymphocytes in the vitreous, and infiltrates that lie below the retinal pigment epithelium and neural retina. Vitreoretinal lymphoma is considered a subtype of primary central nervous system (CNS) lymphoma,<sup>3</sup> and over time approximately 70% of affected individuals develop extraocular lymphoma.<sup>4</sup> Intracranial involvement determines survival: recent population-based studies from high-income countries provide 5-year survival estimates of close to 30%.<sup>5–7</sup>

Vitreoretinal lymphoma presents diagnostic and treatment-related challenges. The cancer frequently masquerades as intraocular inflammatory disease—termed uveitis—and patients may initially be treated with corticosteroid and other immunomodulatory



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drugs.<sup>1</sup> The gold standard for diagnosis is cytology and flow cytometry, performed on ocular samples that are obtained by vitrectomy.<sup>8</sup> However, the diagnosis often remains elusive as cells are scant and fragile, and lymphotoxic immunomodulatory therapy may compound this problem. Chorioretinal and endorectal biopsies are more likely to lead to the diagnosis, but are considerably more invasive procedures.<sup>9</sup> Genetic analyses and cytokine testing of the ocular samples, and ophthalmic imaging are being used variously in an attempt to improve diagnostic accuracy.<sup>10–14</sup> Diverse treatments are used for vitreoretinal lymphoma, including intraocular and systemic chemotherapy, external beam ocular irradiation and autologous stem cell transplantation: a 17-centre European study documented over 25 different treatment schedules in 78 patients.<sup>15</sup> There is a limited medical evidence across treatments, however, and the role of ocular- versus extraocular-directed treatments continues to be debated.<sup>16</sup> An additional long-standing problem for the field is the lack of standard definitions for response and minimal residual disease,<sup>17</sup> despite international workshops on vitreoretinal lymphoma.<sup>18–21</sup>

While there is a considerable interest in improving the management of vitreoretinal lymphoma within the ophthalmology community, a major barrier to moving ahead with this goal is the rare nature of the condition. The prevalence of primary CNS lymphoma has been estimated recently at 0.4–0.5/100 000 person-years,<sup>7 22 23</sup> and vitreoretinal lymphoma is the presentation in only approximately 10% of these cases.<sup>4</sup> Thus, to date clinical trials on diagnostics or therapeutics for vitreoretinal lymphoma have been limited to small and largely retrospective case series. To counter this issue and address the unmet medical needs around vitreoretinal lymphoma, we designed an international registry that would collect diagnostic and treatment data, and record outcomes, to establish new evidence for the management of this cancer.

## METHODS AND ANALYSIS

### Project development

The International Vitreoretinal B-Cell Lymphoma Registry is an investigator-initiated and -led research project that is being implemented to provide an evidence-base for diagnostic testing of and therapeutic approaches to vitreoretinal lymphoma. The concept of an international registry for vitreoretinal lymphoma was presented in 2013.<sup>24</sup> Subsequently, an international group of subspecialised ophthalmologists came together to identify 20 key clinical data items that would be collected. Customised software was developed to permit the collection of these data, using a WordPress-based platform, with engineering services provided by Techland Design (Thames, New Zealand). Following ethics review and approval by the Royal Australian and New Zealand College of Ophthalmologists Human Research Ethics Committee, the registry was launched in 2021 under a uniform resource locator (<https://www.internationalVRLregistry.org>).

### Patient and public involvement

The registry was designed by clinician-researchers without the input of patients and the public, given that the initial motivation was the lack of definitive diagnostic and treatment information to guide clinical decision-making in vitreoretinal lymphoma. However, following the first period of data analysis, data collection will be expanded and at that time, opportunity will be taken to involve patients and patient support persons in guiding changes. Areas that will benefit considerably from patient comment include outcome measures, with particular focus on ocular and extraocular symptomatology of the cancer and its treatments, as well as time intervals for data collection. In addition to medical dissemination (discussed later), results of the registry may be shared in internationally accessible media targeted to the general public (eg, *The Conversation*<sup>25</sup>) and social media forums (eg, *Eye Care Community*<sup>26</sup> and *r/eyetriage*<sup>27</sup>). Development of resources for patients and support persons is being undertaken as an independent project in parallel with the registry, with resources to be made publicly available through a dedicated webpage of the patient-focused partner organisation, South Bank Day Hospital (Brisbane, Australia).

### Project structure

The International Vitreoretinal B-Cell Lymphoma Registry is an international collaborative research project. The coordinating centre is based at Flinders University. This centre is responsible for sourcing the registry software, including updates, for coordinating data collection, including reviewing and correcting the data, and for performing and synthesising data analyses. Registered investigators at individual sites are responsible for identifying patients for enrolment into the registry and the entry of clinical data, in accordance with the project protocol. Early in the project, a steering committee was convened by JRS for the express purpose of determining the data items that should be collected by the Registry (members: JLD, JHdB, AJH, MM, HNS, JRS, HT, NHtD-vL, VT, DVV-S, DJW, SY). With launch of the registry, a new steering committee is being formed to provide ongoing research leadership. This committee will be responsible for direction and strategy, resources and funding, oversight for data management, and drafting of publications, with membership to cover expertise in clinical care, human research ethics and data management.

### Investigator recruitment and registration

The registry is open to all ophthalmologists in all countries for participation as an investigator. However, most investigators who contribute data to the registry will be ophthalmologists who subspecialise in the management of vitreoretinal lymphoma, including ocular oncologists, vitreoretinal subspecialists and uveitis subspecialists. Launch of the registry was announced on the chatlines of the American Uveitis Society, the Royal Australian and New Zealand College of Ophthalmologists Uveitis Special

Interest Group, the International Ocular Inflammation Society and the International Uveitis Study Group, with an invitation for ophthalmologists to register their interest. Invitations will continue to be made periodically through these and similar professional organisations.

Since launching the registry, we have received 142 expressions of interest from ophthalmologists in 37 countries. After interest is registered, ophthalmologists receive an email that provides a brief introduction to the project. Since human research ethics approval is Australia-based, potential investigators who reside outside Australia must seek local human research ethics review. They receive copies of the Royal Australian and New Zealand College of Ophthalmologists Human Research Ethics Committee approval notification and the approved protocol, with the offer of assistance in preparing their submission. Investigators must confirm local human research ethics committee approval, or formal waiver of this need, prior to being provided access to the registry platform. Australian ophthalmologists, or ophthalmologists outside Australia with human research ethics approval, receive a welcome email with user instructions, and two additional emails with registration details and a temporary password. To date, 26 ophthalmologists in 13 countries outside Australia have completed the required local human research ethics committee review and, along with 19 Australian ophthalmologists, are registered investigators on the project.

### Registry population

Patients aged 18 years and older, with a diagnosis of B-cell vitreoretinal lymphoma that has been diagnosed from 1 January 2020 onwards, are eligible for enrolment into the registry. The lymphoma may be of new onset, or it may represent the recurrence of previous lymphoma, and it may be isolated to the eye or be associated with lymphoma in other regions of the CNS or elsewhere in the body. Recognising the challenges in making the diagnosis of vitreoretinal lymphoma, the registry allows for a diagnosis made on the basis of molecular markers alone, and a diagnosis extrapolated from extraocular CNS involvement, as well as lymphoma that has been confirmed by cytology of ocular samples per gold standard. While this may allow for enrolment of patients who subsequently are found to have another diagnosis (eg, sarcoidosis<sup>28</sup>), there is a route for those patients to exit the registry, and this information will inform on the diagnostic accuracy of different methods.

### Data collection

All clinical data collected in the registry will date from 1 January 2020, and to realise the goal of the project, data will be collected for at least 5 years into the future from that date. The platform has been designed for the collection of data at 3-month 'reporting intervals' to avoid the use of specific dates, which are identifiers in some countries: in any given year, reporting intervals are: 1 January to 31 March; 1 April to 30 June; 1 July to 30 September;

and 1 October to 31 December. Data collection is retrospective, distinguishing right and left eyes. Data may be collected at any time after the end of a reporting interval, and the platform has been designed to be intuitive, to limit the time required for data entry.

The data are collected across a single 'baseline form' and multiple 'follow-up forms' (table 1). The baseline form is associated with the reporting interval during which the patient was diagnosed with active vitreoretinal lymphoma. The baseline data include gender, age at diagnosis, HIV infection, basis for diagnosis, initial disease sites, mode of presentation, and visual acuity and eye tissue involvements at diagnosis. Follow-up forms continue to accumulate until the patient leaves the registry, which may occur due to loss of follow-up, revision of the original lymphoma diagnosis or death. Follow-up data include ocular involvements, ocular procedures, local eye chemotherapy and radiotherapy treatments and complications, extensive extraocular treatments and complications, eye and systemic cancer status, and last recorded visual acuity. Conditional fields are used to limit data omissions. In addition to defined fields, 'other' is included as an option, with a free-text box to allow clarification.

After data entry is completed on any form, the ophthalmologist is taken to a 'review page' to check the data, and after making any required final corrections, they submit the form. After submission, further editing by the ophthalmologist is not permitted to ensure a form is not inadvertently overwritten. However, subsequently the data are checked at the coordinating centre, and corrections can be made in consultation with the ophthalmologist through administrator access to the software platform.

### Data analyses

As the registry collects longitudinal information over time, the focus of the data analyses will change. Initial analyses will focus on defining current practice patterns using baseline and short-term follow-up data. Clinical questions will include: (1) what is the spectrum of clinical manifestations of vitreoretinal lymphoma, including extraocular involvements? (2) which methods are most commonly used to make the diagnosis of vitreoretinal lymphoma (including sites for tissue biopsy)? and (3) what are the most commonly employed treatment modalities for vitreoretinal lymphoma and their complications? We will also determine present definitions of response to therapy, which are relevant to interpreting clinical data. The International Primary CNS Lymphoma Collaborative Group guidelines define complete remission as absence of cells in the vitreous and resolution of any retinal or optic nerve lesions.<sup>18</sup> Many ophthalmologists do not use these guidelines given that some of the ocular pathology observed in vitreoretinal lymphoma is inflammatory or degenerative in nature.

There are no survival data for vitreoretinal lymphoma specifically, but recent studies suggest median survival of primary CNS lymphoma is approximately 2 years.<sup>5 7 22</sup> It is expected that lymphoma which presents first in the eye,

**Table 1** Data that are collected for each patient entered in the International Vitreoretinal B-Cell Lymphoma Registry

Item	Options (if relevant)
<b>Baseline form</b>	
Patient demographics: gender; age at diagnosis; country of treatment; HIV infection status	
Basis for first diagnosis	Cytology; immunophenotyping (immunocytochemistry, flow cytometry); PCR ( <i>IGH</i> rearrangement, <i>MyD88</i> mutation); cytokine analysis (interleukin 10, interleukin 10:interleukin 6)
Initial disease site	Eye; brain parenchyma; spinal cord parenchyma; leptomeninges (including cerebrospinal fluid)
Mode of presentation	New onset disease; recurrent disease
Tissue involvement	Vitreous; retina (including retinal pigment epithelium); optic nerve; anterior segment
Visual acuity at presentation in Snellen (metres, feet or decimal) or Logmar	
<b>Follow-up form</b>	
Tissue involvement	Vitreous; retina; optic nerve
Visual acuity at end of interval in Snellen (metres, feet or decimal) or Logmar	
Vitrectomy	Number
Focal ocular treatment	Intraocular methotrexate (number of injections and dose); intraocular rituximab (number of injections and dose)
Ocular irradiation	Number of treatments and dose
Complications	Keratopathy; cataract; raised intraocular pressure/glaucoma; uveitis; retinopathy; maculopathy
Ocular status	Complete response; partial response; stable disease; progressive disease
Extraocular involvement	Brain parenchyma; spinal cord parenchyma; leptomeninges (including cerebrospinal fluid)
Extensive treatment	Systemic chemotherapy; intrathecal chemotherapy; whole brain radiotherapy; stem cell transplantation
Complications of extensive treatment	Leukoencephalopathy; myelosuppression; infection; hepatotoxicity; ileus
Status at end of interval	Alive; deceased; unknown; revised/non-lymphoma diagnosis
If deceased: age at death; cause of death	
Options include 'other', with boxes provided for free text.	

will progress to involve the CNS over 2–3 years.<sup>4</sup> With the start of data collected within the registry set at January 2020, there should be sufficient data for assessment of survival by late 2025. Clinical questions will evaluate the impact of treatment on visual acuity outcomes, as well as progression to CNS involvement and survival outcomes, addressing the following issues: (1) do local or extensive, or the combination of local and extensive, treatment(s) achieve superior outcomes in vitreoretinal lymphoma? (2) of the local treatments used for vitreoretinal lymphoma, is there a difference in outcomes between chemotherapy and radiotherapy? and (3) given that chemotherapy with methotrexate and/or rituximab is the most frequent local treatment, do outcomes differ for these agents and their combination?

For statistical analyses, continuous data will be described as mean and SD, or median and range, depending on data distribution, and categorical data will be described as totals with percentages. Descriptive statistics will be used for generating an overview of clinical presentations, and diagnostic and therapeutic preferences. Associations between clinical presentations, and diagnostics and treatments, and between diagnostics and treatments, and complications will be assessed by ORs with 95% CIs.

Survival analyses—particularly Kaplan-Meier estimates—will be performed for vision loss, progression-free and overall survival, and ocular and systemic complications, with time-to-event defined as the number of 3-month reporting intervals from diagnosis.

### Data management

The registry platform is protected by clinical firewalls, hosted by South Bank Medical Group, which is an ophthalmology-focused health promotion organisation based in Australia. Within the registry, data are saved in Microsoft Excel spreadsheet format, allowing ready export for external analysis using SPSS Statistics and other statistical software packages. Online access to the platform is by user-specific password, with differential access for 'administrators' (coordinating centre-based researchers) and 'users' (individual site-based ophthalmologists). Coordinating centre staff have access to the total of the data in the registry, and they will be responsible for conducting statistical analyses. Ophthalmologists have access to all data that they have entered, and are able to export data summary spreadsheets. Access to data also will be provided to auditing bodies, such as the Royal Australian and New Zealand College of Ophthalmologists



Human Research Ethics Committee. No patient identifying information is held within the registry. Patients are identified by a unique 6-integer number, which begins with an ophthalmologist-specific 3-integer number, and thus, ophthalmologists must hold a record of patient identities separately.

## DISCUSSION

This paper reports the development of an international clinical registry that will provide real-world data around course, management and outcomes of vitreoretinal lymphoma. By taking a multinational, multi-centre approach, we will counter the low prevalence of this cancer, which is the primary challenge for research to improve its suboptimal outcomes. The International Vitreoretinal B-Cell Lymphoma Registry is disease-specific, including key diagnostic and treatment items, and tracking the two eyes separately. A key design feature of this registry is the use of reporting intervals in preference to dates, since dates may provide clues to individual identities.

In addition to tracking outcomes against different treatment modalities, the registry will provide the material needed to address important controversies related to the diagnosis and management of vitreoretinal lymphoma. There has been much debate about the methods used for the diagnosis of vitreoretinal lymphoma. While cytology has been required traditionally, the negative predictive value has been estimated at approximately 60%,<sup>29</sup> which may delay the diagnosis and require multiple sampling procedures.<sup>30</sup> Some experts question the absolute requirement of cytological confirmation and suggest other molecular tools may be appropriate when the presentation is highly suggestive.<sup>31,32</sup> The registry can address this controversy by tracking modes of tissue sampling and testing, and identifying misdiagnoses. Another unanswered question is the role of intraocular chemotherapy, particularly when there is no extraocular involvement. Locally delivered therapies may induce ocular remission<sup>16</sup>; yet, it is unclear whether adding extensive therapy improves progression-free or overall survival. The registry can address this question by tracking survival against ocular and extensive treatments. The registry also provides an opportunity to explore the concept of minimal residual disease for vitreoretinal lymphoma.

Clinical registries provide the opportunity to collect data in real-world settings, but there are limitations inherent in this research approach, as described by Tan *et al*<sup>33</sup> in their evaluation of clinical registries in ophthalmology. We must anticipate selection bias, given that ophthalmologist participation is voluntary. Missing information and stenographic errors in data entry are also potential limitations. We are addressing these issues by implementing conditional fields, and with manual data checking by cross-referencing across entries. Another potential criticism is that collected information is restricted to the more common diagnostic and treatment

approaches. However, initially limiting the scope of the data items has been intentional, to build involvement and increase compliance. Moreover, free text boxes allow entry of data relating to tests and treatments that are less commonly used. In a future iteration of the registry, the description of extensive treatments could be expanded to include specification of chemotherapeutic drugs, doses and cycles, and whole brain radiotherapy dose and fractionation.

Despite the low incidence of vitreoretinal lymphoma, there is a considerable professional interest in this cancer, with dedicated sessions at major international meetings (eg, *2020 American Academy of Ophthalmology Annual Meeting*), and international conferences built around this condition alone (eg, *2019 Inflammatio*). This fact, in combination with exponential developments in imaging and drug delivery within ophthalmology, and molecular diagnostics and biological therapies within lymphoma oncology, ensure that the field continues to explore new approaches. Thus, we anticipate that scope of the data collected in the registry will grow as the project gathers momentum.

## Ethics and dissemination

Given the anticipated national reach of the registry within Australia, and its ophthalmic focus, application for ethics review was submitted to the Royal Australian and New Zealand College of Ophthalmologists Human Research Ethics Committee. The project received Australia-wide approval, including a waiver of consent to collect non-identifiable patient data (Reference: 109.20, Date: 18 August 2020). Sites located outside Australia are required to seek local human research ethics review; approval or waiver of that requirement is a condition for non-Australian ophthalmologists to be given access to the registry platform. In keeping with the approval, the project will be conducted in compliance with the Australian National Statement on Ethical Conduct in Human Research.<sup>34</sup>

Research results generated through the registry will be disseminated primarily by peer-reviewed publications. These publications are expected to inform clinical practice, as well as educational materials for patients and support persons. Results may also be presented at international clinical meetings and patient-directed forums. Authorship of publications will be attributed to the research group, including the ophthalmologist investigators and other research staff.

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