The ROYAL COLLEGE of OPHTHALMOLOGISTS

REVIEW ARTICLE

The role of a multicentre data repository in ocular inflammation: The Ocular Autoimmune Systemic Inflammatory Infectious Study (OASIS)

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In the current literature, clinical registry cohorts related to ocular inflammation are few and far between, and there are none involving multi-continental international data. Many existing registries comprise administrative databases, data related to specific uveitic diseases, or are designed to address a particular clinical problem. The existing data, although useful and serving their intended purposes, are segmented and may not be sufficiently robust to design prognostication tools or draw epidemiological conclusions in the field of uveitis and ocular inflammation. To solve this, we have developed the Ocular Autoimmune Systemic Inflammatory Infectious Study (OASIS) Clinical Registry. OASIS collects prospective and retrospective data on patients with all types of ocular inflammatory conditions from centers all around the world. It is a primarily web-based platform with alternative offline modes of access. A comprehensive set of clinical data ranging from demographics, past medical history, clinical presentation, working diagnosis to visual outcomes are collected over a range of time points. Additionally, clinical images such as optical coherence tomography, fundus fluorescein angiography and indocyanine green angiography studies may be uploaded. Through the capturing of diverse, well-structured, and clinically meaningful data in a simplified and consistent fashion, OASIS will deliver a comprehensive and well organized data set ripe for data analysis. The applications of the registry are numerous, and include performing epidemiological analysis, monitoring drug side effects, and studying treatment safety efficacy. Furthermore, the data compiled in OASIS will be used to develop new classification and diagnostic systems, as well as treatment and prognostication guidelines for uveitis.

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INTRODUCTION

Uveitis is a complex intraocular inflammation that may be associated with a wide range of different conditions including systemic diseases, and is certainly affected by an interplay between genetic, geographical, and ethnic factors. Although there has been considerable progress in understanding the clinical epidemiology of ocular inflammatory diseases and their treatment [1–3], including breakthroughs in new treatments such as biologic therapy [4–6], there remain open questions regarding important aspects of the diagnosis, investigation, management, and prognostication of these patients. As the field continues to advance, more of such important issues can be expected to arise. Clinical registry cohorts offer opportunities to address these issues in a timely manner [7, 8].

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With the rise of information technology, establishing and maintaining a clinical registry cohort is increasingly less of a mammoth task and may, in fact, eventually become the new standard for such a complex and heterogeneous group of diseases. There are about 97 clinical registries related to the eye with increasing numbers in the past few decades [9]. However, in the current literature, clinical registry cohorts related to ocular inflammation are few and far between [1, 10] and there are none involving multi-continental international data. Many existing registries comprise administrative databases, data related to specific uveitic diseases, or are designed to address a particular clinical problem. The existing data, although useful and serving their intended purposes, are segmented and may not be sufficiently robust to design prognostication tools or draw epidemiological conclusions in the field of uveitis and ocular inflammation.

Here, we discuss the usefulness and advantages of a comprehensive multicentre clinical registry cohort in ocular inflammation, which collects data on patients with both infectious and non-infectious uveitis, and describe the methods of the Ocular Autoimmune Systemic Inflammatory Infectious Study (OASIS) registry as a platform that will serve this purpose.

METHODOLOGY

Proposed model—the OASIS clinical registry

The OASIS Clinical Registry aims to be a comprehensive yet succinct repository of retrospective and prospective longitudinal clinical data related to ocular inflammatory diseases. The main objectives of this global integrated platform is to elucidate the spectrum of uveitis diagnosis and management across the various geographical regions of the world, to develop standardized approaches to diagnosis and management of uveitic disease, prognosticate visual outcomes and ocular comorbidities, offer recommendations for treatment protocols, and eventually, propose digital tools for unifying the diagnosis and management of ocular inflammatory diseases. These objectives will be achieved by clinical epidemiologic analysis of the large and international registry cohort, and the conduct of machine learning and big data analyses of the data and associated images. With these approaches, both hypotheses and machine-suggested patterns can be studied.

Scope of clinical data. The OASIS Clinical Registry collects over time the following clinical data for all affected eyes of all patients in a structured format: demographics, past medical history, past ocular history, infectious and non-infectious specific systemic disease data, clinical presentation, ocular examination findings, investigations, diagnosis, treatment, clinical course, working diagnosis, characterization of ocular inflammatory diseases, anatomical and visual outcome, side effects of treatment, and clinical images. The scope of data is summarized in Appendix 1. Example images of the "Working Diagnosis" (Fig. 1), "Visit Summary" (Fig. 2) and "Course of Disease" (Fig. 3) pages of the OASIS Registry can be found below. Similar clinical information can be collected at the follow up visits. The timing of entries is flexible and new information from all follow-up visits can be entered into the registry as follow-up visits occur over time. The registry supports both retrospective and prospective data entry, and allows clinicians to revisit past information or append new data at each follow-up visit. The standardization of data collection is critical for facilitating comprehensive analysis of the clinical data as well as AI model development. Efforts in integrating clinical data which have been collected in individual center systems are often exhausting and tend to lead to very heterogenous data, which is ill-suited for analysis.

With such a large number of data points being collected, the provision of a birds-eye view of the patient profile that includes the most relevant and salient data points would be useful for clinicians using the platform. The OASIS Clinical Registry has incorporated an "Overview Tab" that can be viewed at the top of the browser once users complete entering baseline data of the patient, as seen in Fig. 4. Furthermore, the "Overview Tab" will also include the differential diagnoses that may be considered for the patient given the data points entered, based on the latest SUN classification criteria for uveitic conditions [11–35]. The tab appears at the top end of the screen at all times.

The data points included for collection in the OASIS registry were subjected to multiple rounds of consideration by the study team prior to finalizing the most pertinent clinical information needed. This was to ensure that the data form would be kept as short as possible without sacrificing salient clinical points.

The OASIS clinical registry has also incorporated an image repository that will pave the way for future image-based machine learning classifications and diagnostic criteria and may help enhance current classification systems. The types of images collected include fundus photographs, anterior segment photographs, fundus fluorescein angiography (FFA), indocyanine green angiography (ICGA), optical coherence tomography (OCT), optical coherence tomography angiography (OCT-A), and ultrasound images. After a sufficiently large number of clinical photographs and associated clinical data are collected, they can be incorporated into machine learning and artificial intelligence (AI) models to develop a tool that will aid in the analysis of future cases. This will be elaborated on in the sections below.

Definitions

The OASIS registry has adopted the Standardization of Uveitis Nomenclature [SUN] Working Group classification for uveitis nomenclature [36]. This includes the anatomical diagnoses and terminology, grading systems, description of the disease course and activity, as well as diagnostic and classification criteria for specific uveitic entities. For the ease of standardized data collection, the basic terminology in the SUN classification proves to be useful and will be incorporated into the OASIS registry. The recently proposed classification criteria for diseases by a subsequent iteration of the SUN group can be applied to the data collected to facilitate clinical epidemiological assessments using the data [11–35].

Features of the OASIS clinical registry

User friendly. The system is intuitive and easy to be used by ophthalmologists and their teams. It provides the required flexibility that enables doctors to capture the most important data while minimizing constraints on their way of working. The system is available on all modern browsers, a platform that is familiar to users world-wide on desktops, laptops, tablets, and other mobile devices.

Accessible. The OASIS Clinical Registry is an easily accessible web-based platform with very modest computing requirements (simple computer with a standard web browser and internet connectivity), allowing it to be easily used in all parts of the world. Signing up for the platform is cost-free and simple. All centers in a variety of settings, from primary, secondary to tertiary, are welcome to participate. These features reduce collection barriers and help capture data from less represented regions of the world to provide a more comprehensive and holistic representation. It also provides new insights into the clinical epidemiology of ocular inflammatory diseases in these areas, which might not be accessible otherwise.

All-encompassing. The OASIS Registry is unique in the field of ocular inflammation, as it is the first registry to collect data on all uveitic entities. Data is collected on a wide range of ocular inflammatory disease, including both infectious and non-

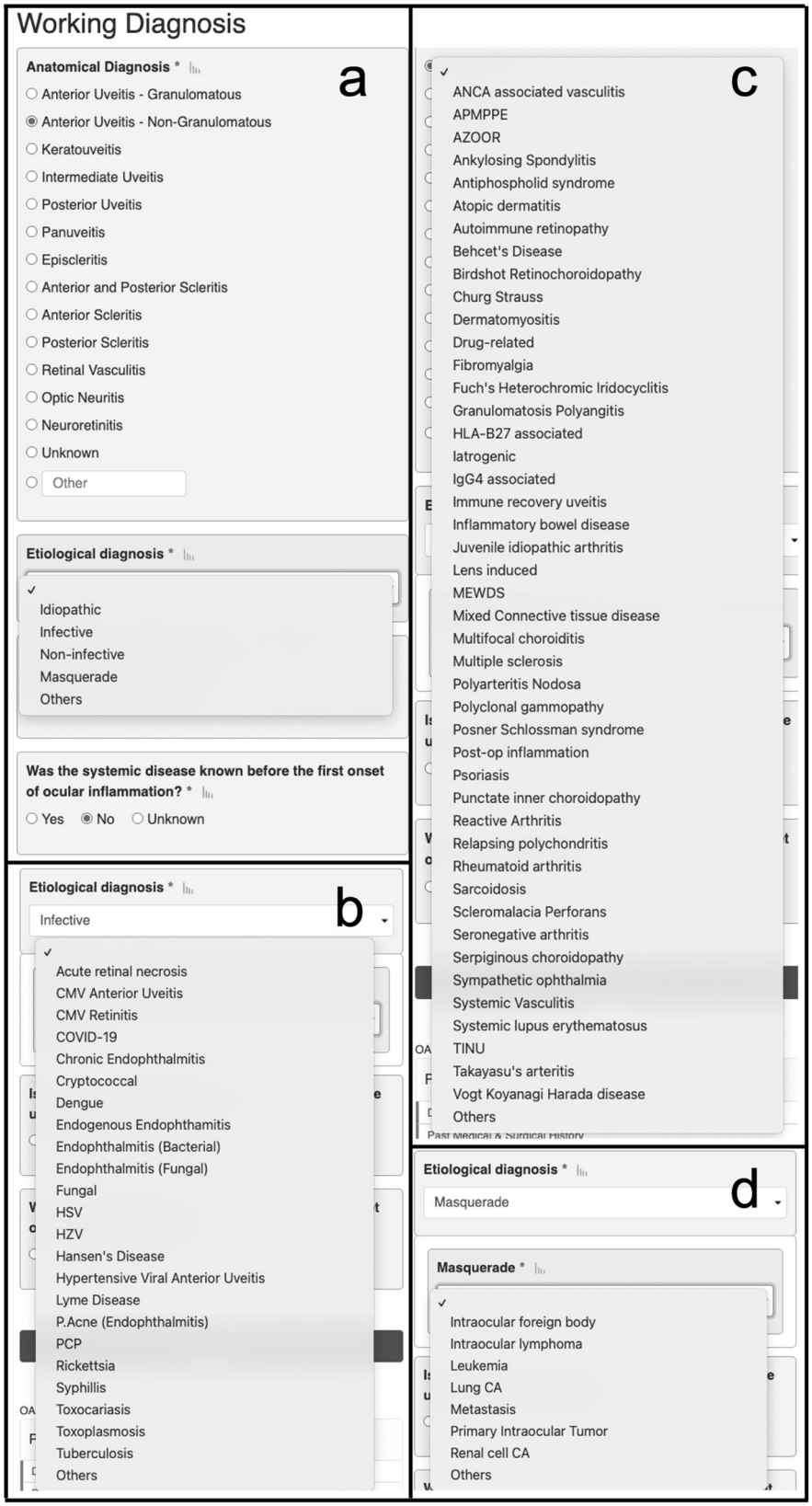

Fig. 1 A screenshot displaying the data points collected on the Working Diagnosis page of the OASIS Clinical Registry. a Diagnoses are grouped into infective, non-infective, masquerade and others. **b** The list of infective aetiologies that appear once "Infective" is selected as the etiological diagnosis. **c** The list of non-infective aetiologies that appear once "Non-infective" is selected as the etiological diagnosis. **d** The list of masquerade diagnoses that appear once "Masquerade" is selected as the etiological diagnosis.

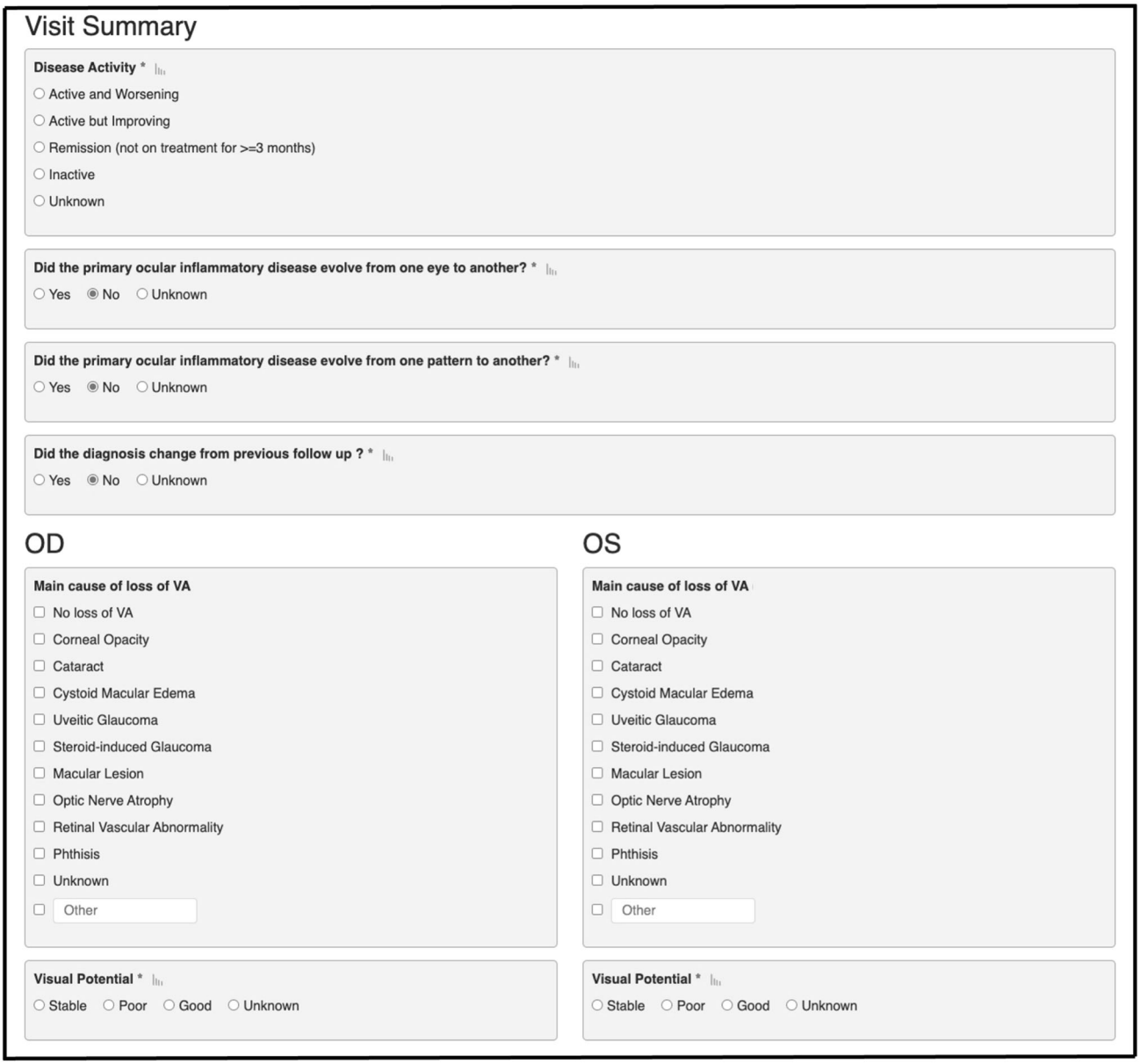

Fig. 2 A screenshot displaying the data points collected on the "Visit Summary" page of the OASIS platform. These include data on disease progression, as well as the main cause of vision loss and visual potential of each eye. OD oculus dexter, OS oculus sinister.

infectious conditions, from a diverse group of participating centers in an all-inclusive manner. Centers from different geographical locations, urban and rural settings, serving populations with varying demographics are included in the registry. This inclusiveness will allow uveitic diseases with unique geographical distributions to be studied, comparing the contexts. For example, a similar approach in the Collaborative Ocular Tuberculosis Study has allowed us to leverage information of ocular tuberculosis cases from endemic and non-endemic areas to generate clinical recommendations pertinent to each [37].

Smart features. In addition, the registry is equipped with user-friendly "smart" features that allows users with limited clinical experience to perform data entry. These "smart" features include diagnostic calculators, treatment algorithms, prognostication tools, and a novel image-based registry. Furthermore, automated differential diagnoses may be generated based on the clinical information entered, which may help clinicians differentiate between the uveitides and help assist the clinician in deciding if further investigations are required. The OASIS group also envisions a treatment and prognostication tool that may help clinicians decide on the appropriate management for their patients based on the clinical information entered onto the registry. Appendix 2 illustrates example of one of the patient with details entered on the OASIS platform.

Data management

The OASIS Registry primarily involves online data sourcing. For this, we have developed the online web-based OASIS Registry system (see Figs. 1–4) to collect data from a large cohort of patients who have received a diagnosis of ocular inflammatory disease. All the patients with uveitis diagnosis can be included in the registry and only those patients who are not willing to consent or share their deidentified data to be excluded from the registry. The web-based registry enables doctors to collect de-identified demographic data (without any patient identifiers), patient history

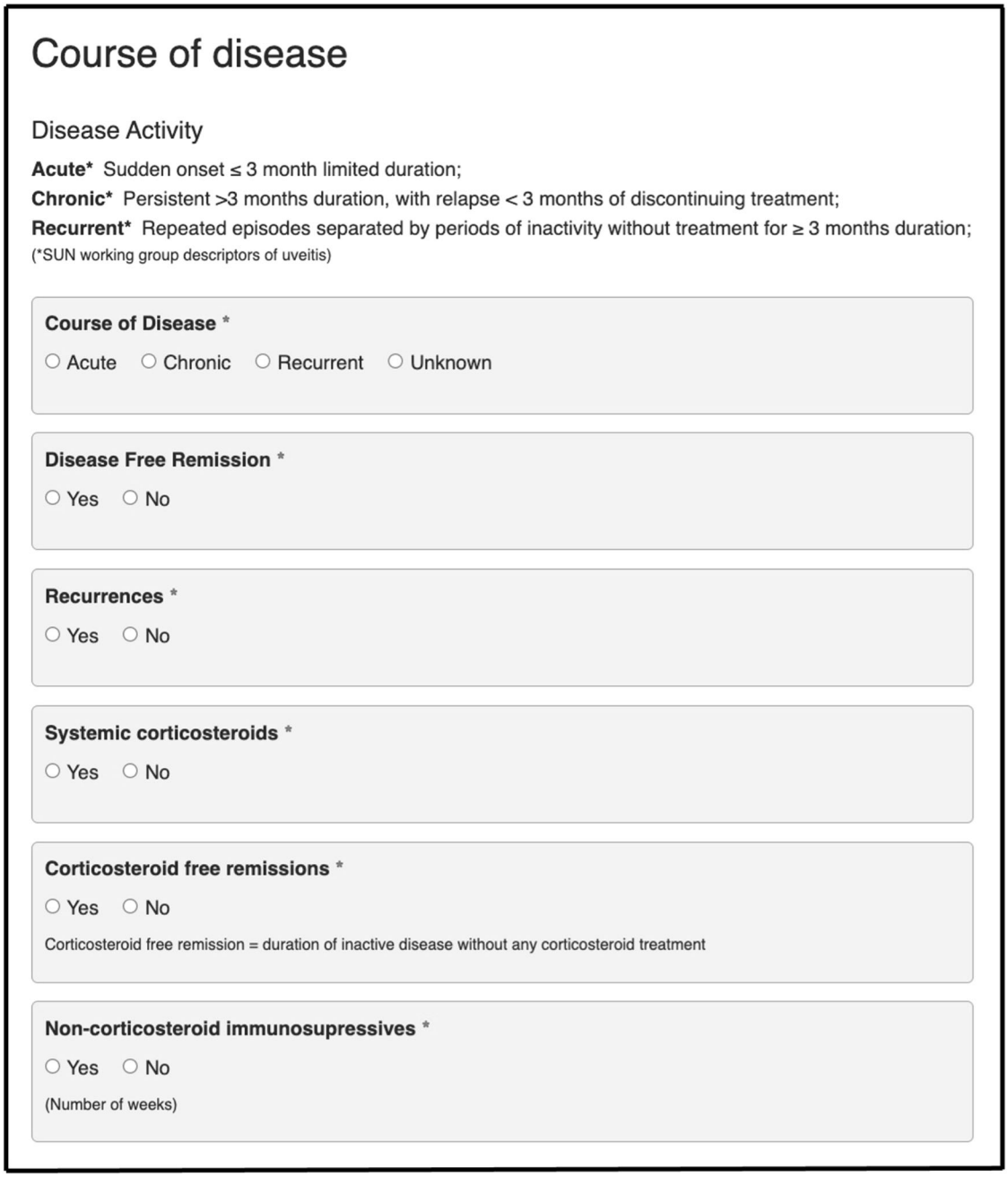

Fig. 3 A screenshot displaying the data points collected on the "Course of disease" page of the OASIS platform. Users may indicate if the disease is acute in nature, chronic or recurrent, and if any immunosuppresants were administered.

and clinical information at the start of the study and during follow-up. Variables that are collected are detailed in Appendix 1.

User access to the registry will be restricted by username/password and is managed by the platform administrator. A cloud infrastructure has been developed and supported using Amazon Web Services (AWS) [Seattle, Washington, United States], and the platform has been deployed and configured on AWS. The platform will be scaled to meet the traffic and storage needs as the study progresses in scale.

In terms of scalability, the OASIS Registry is built to handle a very large volume of data, including patient records and images. Therefore, the web-based platform that the OASIS registry is hosted on is scalable from a computing and storage perspective. The registry leverages a cloud-based platform to achieve scalability of infrastructure. The solution design has been built on containerization and microservices such that the system can scale at any layer in the cloud environment.

Data security

While the OASIS Registry handles de-identified patient data, it still must be secure. The system implements different security strategies for data in transit and data at rest, such that even the de-identifiable patient's information is not compromised to users and administrators of the system. The system uses secure Hypertext Transfer Protocol Secure (https) and Internet Protocol Security (ipsec) based communication and deploys encryption technologies for realization of these objectives. The users of the system will be authenticated using OAuth (OAuth is an authentication protocol that allows users to approve one application interacting with another on their behalf without

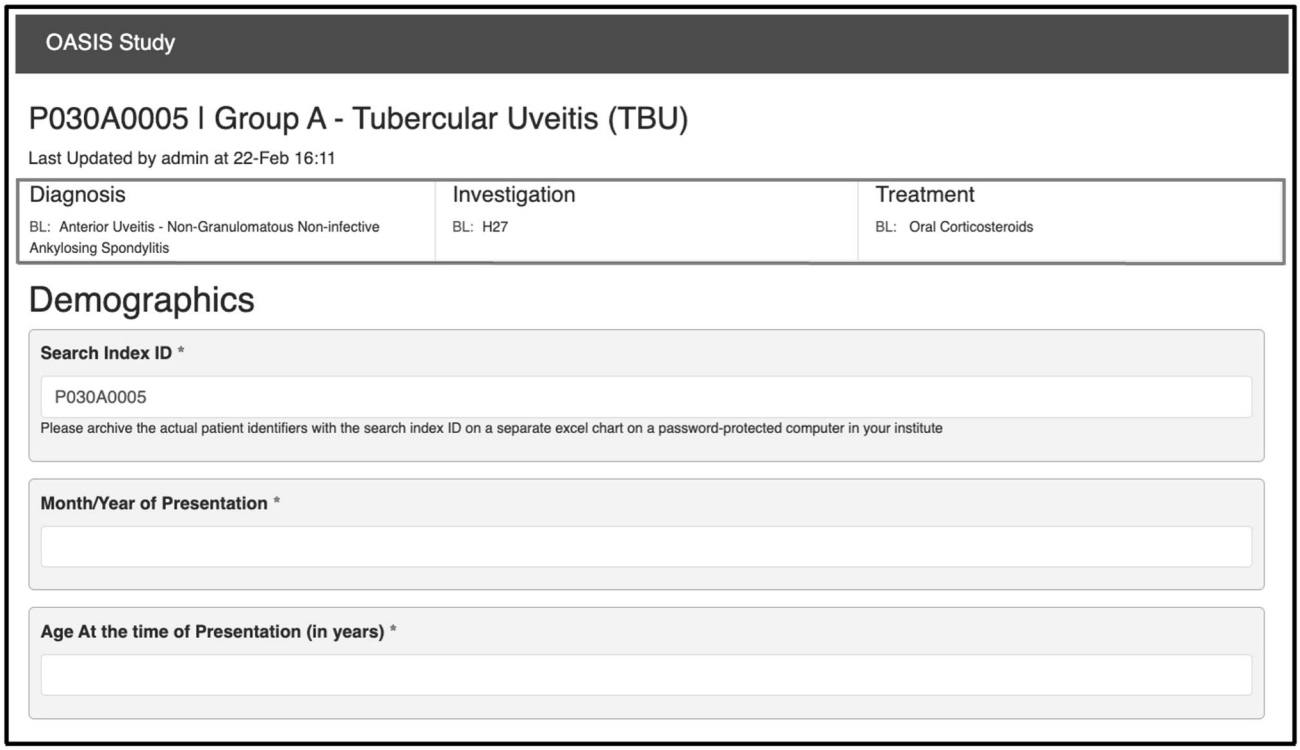

Fig. 4 A screenshot of the Overview Tab (boxed in red) shown at the top of each patient record. This easily accessible summary of patient details provides users with a useful overview of the patient's profile.

giving away the password) and multifactor authentication for additional security.

To facilitate auditing and tracing, all changes to the OASIS Registry will be journaled so that the data can be tracked to check who made what changes when and for what purpose.

Image-based registry

Many ophthalmological diagnoses rely on clinical signs. With the advent of high-tech and high-resolution ocular imaging and fundus photography, we aim to use machine learning to produce image-based classification. Other imaging techniques such as OCT, FFA, ICGA, and OCT-A are more widely available and serve both diagnostic and therapeutic purposes. The utility of such an image-based classification may also be further expanded to treatment algorithms as well as criteria for the monitoring of disease course and activity.

The aim of the OASIS image registry is to aid in the diagnosis of uveitic conditions, help clinicians differentiate between clinical conundrums and help prognosticate disease outcome. Incorporating deep learning and informatics into the image database may provide robust tools that help diagnose and categorize severity of disease. Such tools may be a useful tool for primary and secondary eye centers where there may be a lack of uveitis specialists. The image bank can also be made available for teaching and research purposes and help in the advancement of knowledge for rare uveitic conditions.

We have set up an image bank that allows participants to upload patient images at every visit. The platform supports images in.jpeg and. dicom formats, and will perform automatic tagging of images with patient visits for easy searching and access. The ease of image collection coupled with the multicentre nature of the registry will enable the collection of a large number of images. This will be critical in the generation of robust AI models which frequently requires thousands of images.

Alongside this image bank, we have also set up an image viewer that allows doctors to display, pan and zoom images. Additionally, doctors will be able to add comments and contextual data for the uploaded images. Participants who do not already have imaging repositories may use OASIS for this purpose as well as advancing research objectives.

Image processing and AI models

Since the visual inspection of image-based attributes on fundus images requires the specialized training of an ophthalmologist, this challenges the basic notion of scaling up the ocular inflammation screening program in the absence of sufficient availability of uveitis experts. We propose to use an end-to-end deep learning-based approach for differential diagnosis of ocular inflammatory diseases using clinical images from patients. This component of the architecture will be responsible for the development of algorithms and AI Models based on the dataset collected in the OASIS Registry. We propose to use convoluted neural networks (CNN) architectures such as AlexNet [38], SqueezeNet [39], VGG Very Deep Convolutional Networks (VGGNet) [40], GoogLeNet [41], residual neural network (ResNet) [42], Dense Convolutional Network (DenseNet) [43], and Xception [44] to stage each fundus image based on their lesions. We propose to use architecture similar to Siamese neural network models for the auto triaging of left-right pair of images into red-orange-green classes. Here, the objective is to extend the concept of feature shared Siamese twin networks with Faster regions with convolutional neural networks (Faster R-CNN) [45] for simultaneous localization and classification networks relying on global average pooling (GAP) concepts to identify pathological regions in fundus images. Recently developed approaches for integrating image data across multiple study cohorts would also be employed to create an eye specific atlas of anatomical structures in the fundus image and reporting of pathological observations with respect to anatomical bases. The approach consists of the following:

Feature extraction from Images. This stage involves the extraction of key features from the image using various image processing tools and platforms. These include edge detection, pattern

recognition, clustering and cluster analysis, thresholding of color and brightness, noise reduction and image transforms.

To accomplish the above, various tools and techniques will be applied. Examples of such tools include but are not limited to MATLAB (MathWorks, Natick, Massachusetts, USA), Python Libraries, Scikit, OpenCV (Intel, Santa Clara, California, USA), OpenGL and WebGL (Khronos Group, Beaverton, Oregon, USA). Using these tools, we will employ one or more of the following techniques, such as independent component analysis [46], isomap [47], kernel principal component analysis [48], latent semantic analysis [49], partial least squares [50], principal component analysis [51], multifactor dimensionality reduction [52], nonlinear dimensionality reduction [53], multilinear principal component analysis [54], multilinear subspace learning [55], semidefinite embedding [56] and autoencoders [57].

These features are not just useful for the generation of AI models but are also important for associative analyses against the rich clinical data collected to better understand the relationship of the image features with clinical parameters. This could potentially generate new insights into the disease.

Infrastructure. In many cases, the operations require a large computer infrastructure. Therefore, running these computations on a large central processing unit (CPU) or graphics processing unit (GPU) is required.

These algorithms are anticipated to have a computational load of about 20 billion floating point operations per second (FLOP) of FP64 operation estimated based on state of art deep neural networks. Training with 2500 patients imaged on left-right eye for maximal retinal coverage with each image of about 1 megapixel (MP) would put the compute to ~5e14 FLOP requiring compute power of ~100 TFLOPS of FP64 to execute each epoch in 20 s and a moderate estimate of completion of 1000 epochs of training within 6 h. Model training is a very computer-intensive activity. Resources required for creating models exponentially increases as the number of layers and data volumes increases. The system will offload this computation to an AWS platform, a GPU or a TPU hardware for construction of such models.

Feature extraction from data. The data captured in the OASIS Registry will be normalized and quantified such that this information can be used as an additional feature in the AI algorithm. This will be done through a combination of domain expertise and statisticians to collectively make this extrapolation.

Model building. For each of the features to be predicted, we will build a convolutional neural network (CNN) model, each consisting of data preparation and sourcing, splitting the dataset into training and validation sets, adding different layers along with the activation function and compilation of the model with learning rate optimizer and loss function. To train the model, we will need the following five parameters: training data, target data, validation split, epochs and callbacks. For each epoch run, the model will be improved to fit into the target. The model needs to be rebuilt to match new data that comes into the repository and avoid drift.

Model prediction. The generated model is trained to take raw data or images as input and predict outcomes based on its training. In order to determine the accuracy of the model, the matrices that will be accessed are the confusion matrix, sensitivity, specificity, accuracy, Cohen's kappa coefficient, recall, precision and KL-/JS-divergence.

Standards compliance and contribution. The developed algorithms will be assessed to be compliant with (Institute of Electrical and Electronics Engineers) IEEE Standards including P3333.1.2 (Standard for the Perceptual Quality Assessment of Three Dimensional (3D) and Ultra High Definition (UHD) Contents) for visualization of abnormality localization, 1680.2-2012 (IEEE Standard for Environmental Assessment of Imaging Equipment).

Interpretation engine. Different CNN models now need to be assembled together to provide a holistic view of the different predictions that can be done on the input data. It consists of developing an application programming interface (API) layer that will take raw data input, perform feature extraction of images and the processing of the data as was done at the time of training and give the inputs to different CNN models that will provide their classification results. All these results are compiled to form a higher order prediction of the results that are meaningful to the end user. The types of APIs that will be exposed are prediction APIs, image analysis APIs and classification APIs.

Job scheduler. In many cases, the processing of the image and assessment of the predictions would be a time-consuming activity and, therefore, would be done offline via a job scheduler. When the job is submitted it would be stored in a queue and picked up by the job scheduler for processing. The results would be stored back into the database and a notification would be sent to the user for checking the analysed values.

The entire process for data and image processing using AI in the OASIS Registry is represented diagrammatically in Fig. 5.

Infrastructure

API Gateway: The API gateway will provide capabilities to publish, maintain, monitor, and secure APIs for the end users applications, mobile application and devices. The gateway handles all the tasks involved in accepting and processing up to hundreds of thousands of concurrent API calls, including traffic management, authorization and access control, monitoring, and API version management.

End User Web Based Platform**:** A web-based system has been developed to support the interfaces for the end users, this system allows the uploading of images, analysis of the image and patient data via the interpretation engine and reporting of results.

Continuous improvement and Collection of Feedback: The system will collect feedback if any prediction was incorrect or whether it matches the human assessment. This can be done using a star rating system at the minimum along with a more quantified survey results variance. This feedback is taken as input for model generation such that the system improves its efficiency and accuracy over time.

DISCUSSION

Utility of an ocular inflammation clinical registry

Comprehensive centralized data repository. A registry that captures well-structured clinically meaningful data in a simplified and consistent fashion from multiple sites will deliver a comprehensive and well organized data set that is ripe for data analysis. Much of the work in data analytics is in the preparation of data including its collection and subsequent clean-up to get it to an analytically ready form. This is laborious and oftentimes error prone, leading to subpar analysis not because of the methodology but because of the nature of the data. Therefore, a registry of this sort would immediately solve a major hurdle in data analytics. The availability of such a data gold mine would also allow more researchers to actively analyse the data rather than collect their own, which is a time consuming step as mentioned. This would allow for more insights and interpretations to be obtained. This has been clearly observed in large scale data generation projects such as the one thousand genome project [58], the ENCODE (The Encyclopedia of DNA Elements) project [59] and the TCGA (The Cancer Genome Atlas) project [60].

A multicentre approach such as this also expands the diversity of the data collected and provides a much more holistic

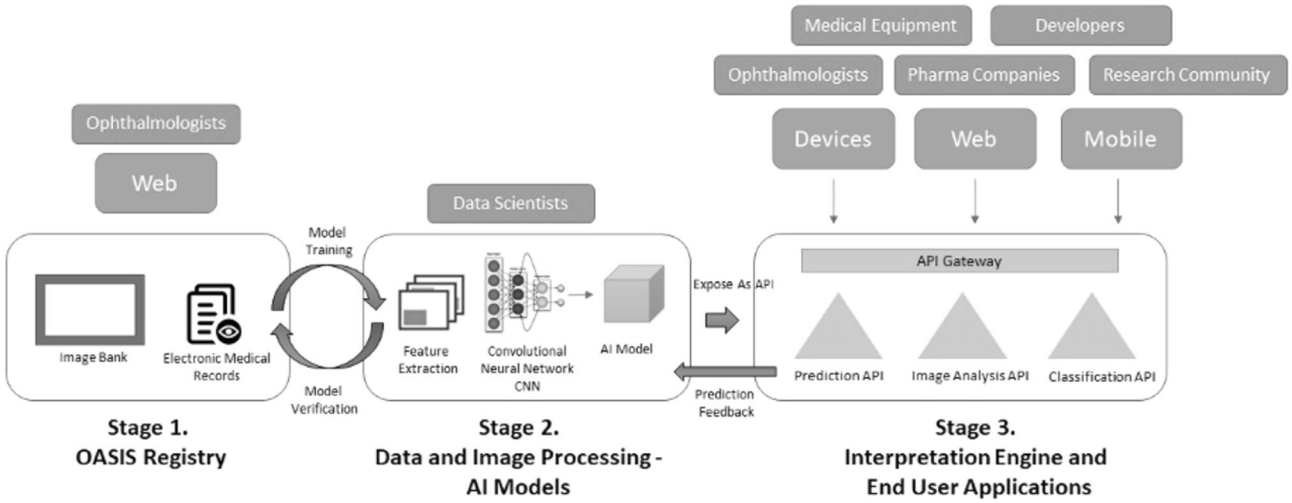

Fig. 5 A diagrammatic representation of the process of data and image processing using artificial intelligence (AI) in the OASIS registry. Data collected from the registry will be utilised to train AI models that may ultimately assist clinicians in diagnosis, prognostication or treatment.

perspective. This is critical for data analytics as it enables a more comprehensive look at the data, allowing us to better understand the various factors which impacts clinical outcomes, such as geographical location and differences in medical practices. Besides providing a more comprehensive insight into the clinical problem, the availability of such a large and rich dataset will also allow for robust AI models. The training of AI models does require large amounts of data and this is something that an international multicentre effort is suitably capable of.

While many registries are set up for rare diseases and specific phenotypic manifestation of diseases, the wide spectrum of ocular inflammation presents multiple uncommon conditions. Pooling the data of individual and specific uveitic conditions can not only help consolidate data within an esoteric entity, but also aid in comparison across uveitic entities and identification of patterns between similar clinical problems. Detailed records of natural history and progression of disease can help us better understand the various patterns of uveitis. This may guide further complementary improvements to current classifications of the uveitides. The SUN classification proves to be a robust method of classification based on anatomical involvement of intraocular inflammation. However, there may be a role for including extraocular inflammatory entities such as episcleritis, scleritis and keratouveitis into the classification, as these are common ocular inflammatory conditions that may overlap with other uveitides. Retinal vasculitis could also potentially be classified as a separate entity from posterior uveitis, as the aetiologies for retinal vasculitis are quite distinct from other causes of posterior uveitis. Figure 6 [61] describes the proposed classification complementing the existing SUN Working Group criteria.

A tool for epidemiological analysis. There is a lack of robust international multicentre data related to uveitis. Certain conditions have strong ethnic and geographical predilection, such as tuberculosis-related uveitis which is more prevalent in endemic regions [62], Vogt-Koyanagi-Harada (VKH) disease which affects ethnic groups who also possess greater skin pigmentation [63], or Behcet's disease which is known to be associated with the "Silk Route," causing genetic predisposition in regions extending from East Asia to the Mediterranean [64]. A clinical registry may help clinicians more easily identify clusters or migration patterns that may aid in diagnosis and complement clinical suspicion based on epidemiological background. The availability of such a well curated and comprehensive data set will also allow more researchers to ask various questions and conduct different types of analyses thereby multiplying the research insights gained.

Classification and diagnostic systems. Many classification tools have been proposed for uveitis. The classification system proposed by the Standardization of Uveitis Nomenclature (SUN) Working Group is the most widely adopted worldwide. It has provided consensus for anatomical classification, grading of disease activity and clinical course [65]. Recently, the SUN working group utilized machine learning analysis of a database of over 5000 patients to validate classification criteria for 25 specific uveitides [66]. The OASIS study group aims to utilize the data from this clinical registry to further expand on the current anatomical classification and propose a broader classification of ocular inflammation that may include overlap syndromes as well as extraocular inflammation. Smart tools such as diagnostic calculators based on the SUN criteria have also been built into the OASIS registry to help classify the types of uveitis entered into the registry, as well as to benefit users in their clinical practice.

From an extensive collection of clinical data points and ophthalmic images of patients with uveitis, an artificial intelligence based diagnostic support tool can be built. Such a tool may be useful in classifying and differentiating between different causes of uveitis. This may facilitate diagnosis and management of uveitis in the setting of an ophthalmology clinic, and may also facilitate the referral of patients to specialist care in general practice settings. Artificial intelligence based image classifiers have already been previously built and validated for conditions such as diabetic retinopathy, age-related macular degeneration and suspected glaucoma [67]. However, none have been developed and validated thus far for the detection of uveitides. In OASIS, we have developed a rules-based classifier that will actively generate a list of differential diagnoses as users enter data into the OASIS registry form, based on the SUN classification for uveitic conditions [11–35].

Investigations. Uveitic conditions often rely on a barrage of laboratory tests for confirmation of diagnoses and ruling out differentials during initial evaluation. Multiple tests may lead to high costs incurred to rule out all infective and inflammatory causes of a particular uveitic presentation. If we could utilize

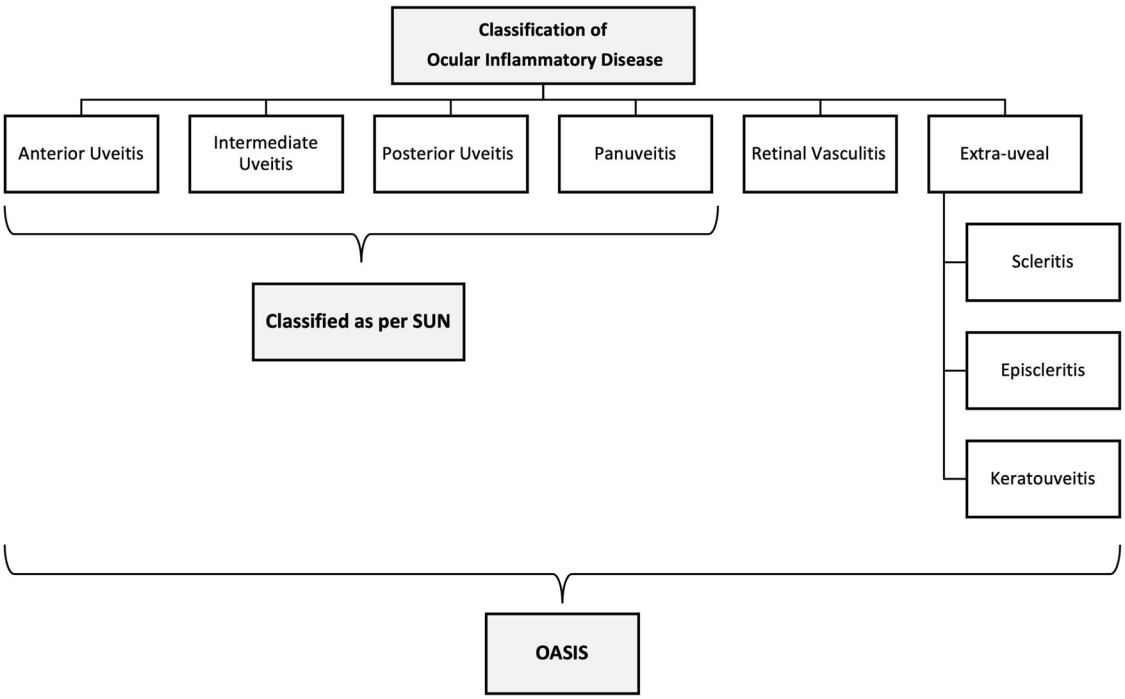

Fig. 6 The proposed OASIS classification complementing the existing SUN Working Group criteria. In the proposed classification, retinal vasculitis is classified as a separate entity from posterior uveitis, and extraocular inflammatory entities are included.

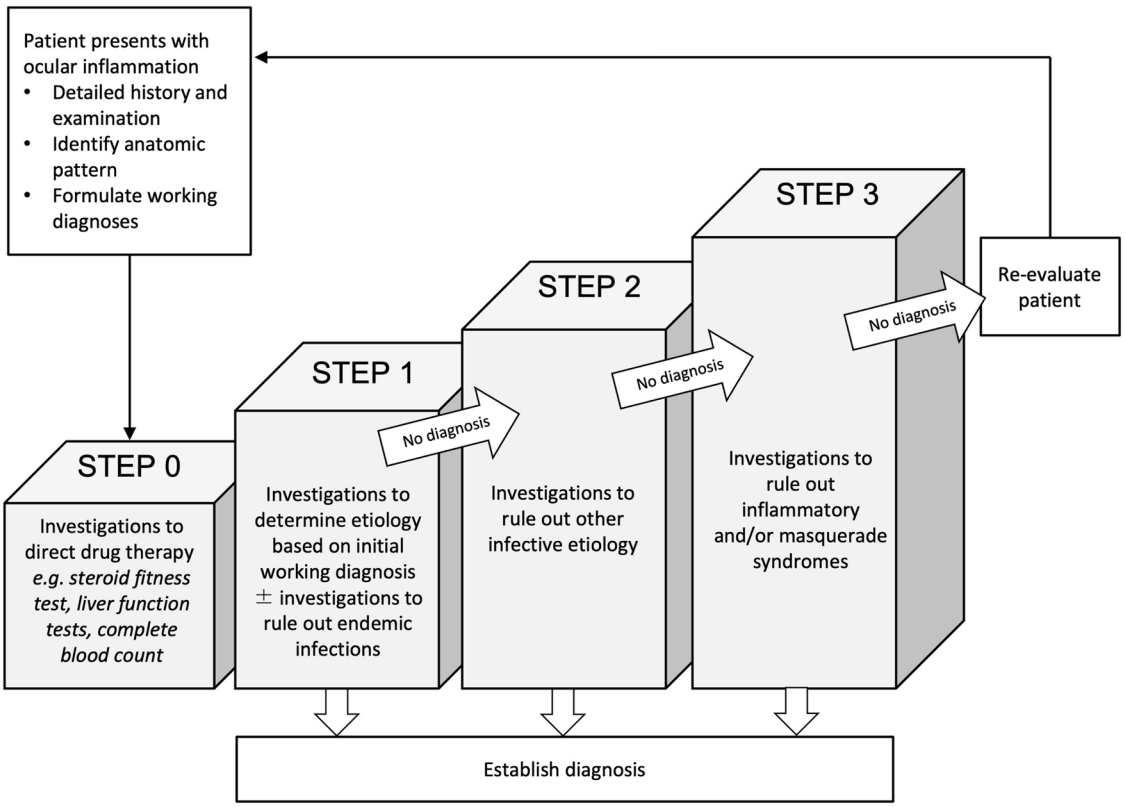

Fig. 7 A diagrammatic representation of a step-ladder approach to diagnosis of uveitic conditions. By utilising this step-ladder approach, the number of investigations performed by clinicians to reach a diagnosis can be reduced, leading to better cost-efficiency.

machine-learning and informatics, investigations could be further streamlined, leading to better utilization of laboratory tests and better cost efficiency. It was shown in OASIS Report 2 that there is a high utilization of autoimmune tests for patients presenting with ocular inflammation despite its limited yield [68]. As such, a step ladder approach (Fig. 7) could be incorporated into a machine learning database to suggest an efficient approach to conducting investigations during initial evaluation.

Treatment and prognostication. The OASIS registry will also act as a platform for the development of treatment and prognostication guidelines and tools. We aim to use the data collected to develop and validate algorithms for treatment and prognostication. Such algorithms could enable users to prioritize differential diagnoses, estimate severity of disease and derive management plans.

Registries are a useful way to develop treatment guidelines in diseases with clinical heterogeneity. For example, the Collaborative Ocular Tuberculosis Study provided a consensus-based guideline for the initiation of anti-tubercular therapy in tuberculosis related uveitis [69]. A clinical registry such as OASIS may help enhance the development of experience-based as well as evidence-based guidelines as it can capture geographical, phenotypic variations and differences in practice patterns.

Another useful application of a registry is the development of objective scoring systems that can guide clinical management. Some well-known examples in the field of medicine are the MELD score for survival in liver cirrhosis [70], the APGAR score [71] and CKD-EPI for chronic kidney disease [72]. In the field of ophthalmology, the OTS score for ocular trauma is an excellent example of a prognostic scoring system for visual outcomes [73]. The development of such a scoring system will prove to be very useful in the field of uveitis, as it can help guide treatment and manage expectations of patients with severe disease.

Side effects and safety efficacy. An additional function of the OASIS registry is to monitor for the side effects and safety of pharmacological treatments used in uveitis conditions. The usefulness of such a function in clinical registries has been demonstrated before. For example, the Systemic Immunosuppressive Therapy for Eye Diseases (SITE) Cohort Study was a retrospective cohort study of approximately 9250 patients with non-infectious inflammatory disease from five tertiary centers in the United States [1]. Using their database, the authors studied if immunosuppressive drugs for ocular inflammation had an undesirable side effect of increasing the risk of mortality and fatal cancer. The authors of the SITE Cohort Study demonstrated how, compared to utilizing randomized control trials or case-control studies, analysing registry data is more cost-efficient, less time consuming and reduces concerns of unethical conduct of treatment trials where adverse outcomes are the primary interest of the study. Furthermore, the ORCHIDEA Registry for JIA-related uveitis is also an effective tool for prospective data collection which has allowed for analysis of safety profile of biologics, and have helped standardize the clinical management of young patients with JIA-related uveitis [74]. The OASIS platform hopes to serve a similar function in monitoring the side effects of treatment.

Potential challenges and solutions

Setting up a clinical registry is not, however, without its challenges. It is implausible that all centers will register every patient with uveitis, due to time constraints conflicting with time taken to enter data. As well as this, patients will be entered if they attend the uveitis service, but straight-forward uveitis cases may be managed in a general or urgent care service e.g., acute anterior uveitis. So, there is a potential inherent bias to collecting patients attending tertiary uveitis service. Also, there are many different electronic medical record systems being used around the world and it is difficult to create an application that can synchronise with all these different systems so that data entry will not be duplicated. For the time being, double data entry will have to be done on a separate platform in order to collect data from different sites. However, this is something that we will try to work on in the future. Ensuring data quality is a mammoth task especially with large data sets, heterogeneity in interpretation of clinical records, and different data entry personnel from multiple centers. We have introduced 'smart' features in the data collection form and adopted standardized nomenclature and grading systems to ensure uniformity in data. However, beyond that, there are other aspects of maintaining a clinical registry that requires a consistent and concerted effort by all participating centers. These are elaborated in the following paragraphs.

Data confidentiality and security. The OASIS registry will contain sensitive data of non-identifiable individuals. Sensitive information including but not limited to HIV status, is pertinent to cases of uveitis related to acquired immunodeficiency syndrome (AIDS) such as CMV retinitis, immune recovery uveitis and co-infections with tuberculosis or syphilis. No identifiable data such as name, national registration numbers, or date of birth will be collected in the database. The OASIS database is hosted on a secure SSL/TLS certificate web-based platform utilizing 2048 bit RSA encryption for end-to-end data security. Access to the registry is password protected with muti-factor authentication.

Data management/offline/online. Some institutions may face restrictions on using an online platform due to institutional policy. To overcome this, we have devised an alternative non-cloud system so the OASIS registry may also be used offline. This system will allow users to integrate the OASIS registry form into their institutional computers. Offline users are able to input and collect the same data points as online users and export the data whenever they wish.

Ethical conduct of research. The pooling of large amounts of clinical data will need to be done in a manner that abides by international standards, in accordance with the Good Clinical Research Practice (GCP) guidelines, and to uphold the tenets of the Declaration of Helsinki. In order to ensure this, all participatory centers will require independent ethics committee/institutional review board (IEC/IRB) approval from the relevant local ethics boards and authorities. All patients involved in the study will have to undergo a protocolized informed consent procedure where the OASIS group will provide a standardized information sheet and informed consent procedure.

Data ownership and governance. With a large number of participating studies expected to be part of the OASIS registry, clear guidelines need to be in place with respect to data ownership. The 'Steering Committee' will act as a centralized governing body and will consist of established uveitis experts from different centers around the world. This will ensure checks and balances on all participating centers where the 'Steering Committee' will initiate a consortium agreement which all participating centers have to agree to and abide by. Appendix 3 presents the template of material transfer agreement between different parties and this agreement regulates the data ownership and governance.

Future applications

The OASIS registry will continue to be developed and improved continuously. In the future, we hope that the platform's uveitis classifier will become a common tool used in ophthalmology clinics globally to aid in the diagnosis, treatment and prognostication of uveitic disease. Furthermore, the application of such a registry may also expand to include educational purposes, where interesting cases collected via the registry may be used in the education of ophthalmology trainees and medical students. There are or there will be other similar or overlapping registries in uveitis. All the various registries have done wonderful work in their region and have collected or will be collecting extremely valuable data. It would hence be a shame not to consolidate the data together to maximize the usage of the data. There is an opportunity to apply for large collaborative grant to conduct some work to help reconcile the data from the various registry to a common data format like OMOP CDM. The process of migrating

the data to a common model would allow for ease of interoperability between the various registries in the future. The collaborative grant could also generate analysis plans to be designed against the common data format. These plans could be realized as programming scripts that can be executed against the common data format. This would allow the various registries to run these scripts to generate analytical results for their own data. A meta-analysis could also be done using the results from the various registries to generate a comprehensive look. So, the various registries would have a set of programming scripts to first convert their data to the common data and then to analyse the data. We will probably aim for a publication on the process and maybe another on the meta-analysis.

CONCLUSION

The proposed all-encompassing clinical registry involving international multicentre data may pave the way for further advancements in ocular inflammation and uveitis, such as the development and validation of image-based classifications, diagnostic and management algorithms, and prognostication tools. The OASIS registry incorporates the recently published SUN classification criteria and translates it into a useful clinical tool through the development of a rules-based auto-classifier based on data entered into the system. The open-access nature of the OASIS registry may provide further insight into epidemiological variations in regions of the world where there is paucity of information about the distribution of uveitides. Future developments may include patient reported outcome measures and a collaborative platform for education and research utilizing the image-based registry.

Summary

What was known before

- Uveitis is a complex group of diseases with varying but often overlapping clinical presentation, symptoms and signs.
- The development of an international registry to build a large cohort of patients with uveitis may act as a catalyst for research within the field.
- Currently existing uveitis registries, while serving their intended purposes, are segmented and may not be sufficiently robust to design prognostication tools or draw epidemiological conclusions in the field of uveitis and ocular inflammation.

What this study adds

- This study describes a proposed model for an international registry for uveitis - the Ocular Autoimmune Systemic Inflammatory Infectious Study (OASIS) Registry.
- By collecting a myriad of data points ranging from demographics, symptoms, signs, disease course and response to treatment in patients around the world with uveitis, a comprehensive and sizeable database can be built.
- The data collected may then be analysed to develop and refine diagnostic criteria, and facilitate the building of artificial intelligence (AI) based models for the diagnosis, prognostication and treatment of uveitis, with the aim of improving patient outcomes.

DATA AVAILABILITY

The datasets generated during and/or analysed during the current study are available from the corresponding author upon reasonable request.

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AUTHOR CONTRIBUTIONS

The authors confirm their contribution to the paper as follows: study conception and design: RA, VG, JHK; data collection: all authors; analysis and interpretation of results: RA, BL, SMSN, RL, JHK; draft manuscript preparation: all authors. All authors reviewed the results and approved the final version of the manuscript.

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COMPETING INTERESTS

The authors declare no competing interests.

ADDITIONAL INFORMATION

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