COTS-I

Collaborative Ocular Tuberculosis Study – Phase 1

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PROJECT OVERVIEW

The Collaborative Ocular TB Study (COTS) group aims to generate a centralized registry of a large cohort of patients who have received a diagnosis of ocular tuberculosis (TB). The first phase of COTS study (COTS-1) is a retrospective cohort study where the information will be obtained from records of events that have occurred in the past, primarily medical records.

The primary aim of this study is to determine the sensitivity and specificity of different clinical signs suggestive of ocular tuberculosis in a large multi-centre sample size of different ethnicities and to find out the sensitivity and specificity of different diagnostic tests in the diagnosis of ocular tuberculosis. A secondary aim is to determine the final clinical and visual outcomes in these patients, the side effects related to anti tubercular therapy (ATT) and the causes for treatment failure.

We hope that this large database of patients will provide reproducible and reliable information regarding the clinical signs that may be indicative of ocular tuberculosis, whether or not the use of ATT helps in reducing the recurrence, and the role of concomitant systemic corticosteroids in patients with ocular TB. This will also help to form the preliminary database for COTS phase 2 study (COTS-2) which will be an international multi-centre prospective study.

PARTICIPATING CENTERS

Site No.	Site Name	Investigators
001	Advanced Eye Centre, PGIMER Chandigarh, India	Reema Bansal
002	Moorfields Eye Hospital, London	Carlos Pavesio, Mark Westcott
003	National Healthcare Group Eye Institute, Tan Tock Seng Hospital, Singapore	Ho Su Ling, Dinesh VG
004	Singapore National Eye Centre, Singapore	Chee Soon Phaik
005	Aravind Eye Care, Madurai, India	S.R.Rathinam
006	Narayana Nethralaya, Bangalore, India	Padmamalini Mahendradas
007	LVPEI, Hyderabad, India	Somasheila Murthy
008	Sankara Nethrayala, Chennai, India	J. Biswas
009	Prabha Eye Institute, Bangalore, India	Kalpana Babu Murthy
010	Shroff Eye Centre, New Delhi, India	Shishir Narain
011	University of Manchester, UK	Nicholas Jones
012	University of Monstair, Tuinisia	Moncef Khairallah
013	La Source Eye Centre, Laussane	Carl P Herbort
014	Department of Clinical Ophthalmology & Eye Health, Central Clinical School, Save Sight Institute, The University of Sydney, Sydney, NSW, Australia.	Peter McCluskey
015	King Khaled Eye Specialist Hospital, Riyadh, KSA	Hassan el Dhibi
016	Luigi Sacco Hospital Milan, Italy	Alessandro Invernizzi
017	Rio de Janeiro, Brazil	André Luiz Land Curi
018	Pierre and Marie Curie University - Paris	Baharam Bodaghi
019	University of Istanbul, Turkey	Ilknur Tugal Tutkun
020	University of Thessaloniki, Greece	Sofia Androudi
021	Northwestern University, Chicago	Debra Goldstein
022	LVPEI, Bhubaneswar, India	Soumavaya Basu
023	Polytechnic university of Marche-Ancona, Italy	Piergiorgio Neri
024	Dr Shroff's Charity Eye Hospital Daryaganj, New Delhi	Manisha Agarwal
025	Ramón y Cajal University Hospital, Spain	Julio J González-López
026	Kanpur Eye Hospital, Kanpur, India	Dr Gaurav Dubey
027	UNMC, USA	Quan Nguyen

028	Scheie Eye Institute, Presbyterian Hospital, Philadelphia, Pennsylvania, USA	John Kempen (Study advisor for data analysis)
029	MDS Bioanalytics, Nagpur, India	Dhananjay Raje (Biostatistician)

STEERING COMMITTEE

Principle Investigators:

Vishali Gupta,

Carlos Pavesio,

Rupesh Agrawal

Co-Investigators:

Robert Grant (Senior Medical Biostatistician, UK),

Quan Nguyen

Advisory Board (for data analytics):

John Kempen

B**iostatisitician:**

Dhananjay Raje

WEBSITE AND PROTOCOL ADMINISTRATOR:

Dinesh Visva Gunasekeran, Singapore

INSTITUTIONAL REVIEW BOARD APPROVALS

The COTS protocol requires all the participating sites to get the approval from local Institute review boards. Data collection shall not be conducted at each site until IRB approval for the site is obtained. In case the institute review board feels that ethical

clearance is not needed for retrospective data entry, the letter mentioning the same may be obtained from the local IRB and provided to the COTS team for record keeping.

Confidentiality of Participant Data

The data for all the patients entered on the web based Cognito forms shall be maintained in accordance with legal regulations and all agreements made with the IRBs. No identification has to be entered in the database and each patient shall be coded. The site PIs shall have the access to decode the patient. Protected health information will be kept secure and will not be transmitted to the collaborating sites, unless an exemption is granted by the governing IRB. All study information collected would be kept in a password-protected web based medium. The excel sheets too shall be kept in password-locked computer. Computers and backup files containing data will be kept in secure site-based locations. After the data entry is complete, the COTS data entry portal will be closed.

AUTHORSHIP POLICY FOR COTS-PHASE 1

The authorship for all papers shall include all the participating investigators. The order of authorship shall include the principle investigators, co-authors and the order for collaborators shall be arranged depending upon the number of cases contributed by each center. In case the journal policy does not allow inclusion of the names for all the authors, the authorship will be based on the Modified Conventional style (i.e., named authors "for" the study group, e.g. Gupta, Pavesio, Agrawal "for the COTS-I Group") shall be followed. The credit roster shall include the entire study Group.

Primary Manuscripts

Primary manuscripts of COTS-I shall have Vishali Gupta as the corresponding author and Rupesh Agrawal as first author, and Carlos Pavesio, Dinesh Gunasekeran, Robert Grant, Aniruddha Agarwal (not necessarily in that order) as co-authors. Other co-authors may be included if approved by the Steering Committee. Dr. Gupta will be the corresponding author for COTS-I publications unless otherwise agreed.

Secondary Manuscripts

Other ("secondary") manuscripts can be initiated by any center, but must be supported by one of the following members of the steering committee: Vishali Gupta, Carlos Pavesio or Rupesh Agrawal. Any one (investigator, a resident, fellow etc) can be first author for a secondary manuscript. All the secondary manuscripts must be approved by the study Steering Committee to avoid the duplication of ideas. After approval to write a manuscript is obtained, the manuscript must be submitted within twelve months, or the Steering Committee can revoke the manuscript.

Named authors will include: the primary writer of the manuscript (first author), the statistician conducting the analysis for the paper (if applicable), Vishali Gupta, Carlos Pavesio, Rupesh Agarwal (not necessarily in that order) and Dinesh Gunasekeran. In addition, two other study staff will included as named authors, selected approximately in proportion to the amount of effort invested in the project. Additional authors may be named with approval of the Steering Committee when appropriate. The specific authorship plan will be proposed at the time of proposal of the manuscript by the first author, and is subject to approval by the Steering Committee.

At the time the manuscript is circulated for final approval, co-authors will have two weeks to respond with their suggestions/ comments; those who do not respond will be deleted from authorship of that manuscript.

The study imposes no restriction upon a center's reporting of its own data. Each center may conduct chart review studies in the same manner as if they were not participating in the COTS project. However, centers are encouraged to use the COTS database resource when appropriate.

Meeting Presentation

Abstracts must be circulated one week in advance of submission so that coauthors have an opportunity to comment before submission. Coauthors may either return comments or may indicate approval of the submission by not returning comments. Abstracts should not be submitted unless the following requirements are met: 1) Final tables and figures are completed; 2) Draft manuscript is completed

ELIGIBILITY

To enter data, select a chart, and confirm that the patient described in the chart is eligible for the study. In COTS-I, we are interested in patients seen between January 2005 and April 2014.

INCLUSION CRITERIA

There are the inclusion criteria for enrollment:

I. All the records of subjects including baseline and follow-up visits with details of ophthalmic examination should be available.

II. Supporting ancillary investigations should be available to the investigator.

III. Patients who have completed a minimum follow-up of one year following the diagnosis shall be enrolled.

IV. Patients with the diagnosis of presumed ocular TB. For the purpose of this study, the following clinical criteria shall be used.

A. **Clinical Signs** suggestive of ocular TB i.e. patient may present with any of these;

a. Anterior uveitis granulomatous, nongranulomatous, iris nodules, ciliary body granuloma

b. Intermediate uveitis Granulomatous, non-granulomatous with exudates in the pars plana/ peripheral uvea/ snow-balls.

c. Posterior and panuveitis: Choroidal tubercle, Choroidal tuberculoma, Subretinal abscess, Serpiginous-like choroiditis

d. Retinitis and retinal vasculitis

e. Neuroretinitis and optic neuropathy

f. Endogenous endophthalmitis and panophthalmitis

g. Scleritis

B. **Investigations** documenting the mycobacterium/ genome

a. Demonstration of AFB by microscopy or culture of *M. tuberculosis* from the ocular fluids.

b. Positive polymerase chain reaction from ocular fluids for IS 6110 or other conserved sequences in *M. tuberculosis* genome.

c. Evidence of confirmed active extra-pulmonary tuberculosis (either by microscopic examination or by culture of the affected tissue for *M. tuberculosis*) or demonstration of mycobacterium tuberculosis in ocular fluids.

C. Corroborative Investigations

a. Positive Mantoux reaction: (Each site shall provide the information about the antigen and the amount of tuberculin injected. Also we shall collect information from each site to specify their methods & interpretation for Mantoux test).

b. Quantiferon TB Gold/IGRA – (We shall ask each centre to specify what is the method they are using and how they interpret).

b. Evidence of healed or active tubercular lesion on radiography of the chest and possibly as diagnosed by radiologist (We will again need diagnostic criteria for each centre for chest X-rays).

D. Exclusion of Other Uveitis Entities In the geographic regions where tuberculosis is low in incidence, other causes of uveitis must be excluded.

Patients fulfilling the criteria A and D + B or C shall be enrolled in the study.

EXCLUSION CRITERIA

Following shall be the exclusion criteria

1. Presence of ocular co-morbidities like central serous chorioretinopathy, diabetic or hypertensive retinopathies. The presence of glaucoma, ocular hypertension and

mild cataract not interfering with the media clarity shall not be an exclusion criteria.

All eligible patients shall be entered either on a web-based data entry form. Each site would have a site ID to allow for password-protected data entry.

DATA ENTRY

Data Master: Dr Dinesh VG.

Data Entry Duration: 1st July 2015 till 15th Sep 2015

The **DATA ENTRY** section involves an online COTS-I form on the cognitoforms database system. Patient identity will be kept confidential, and personal information will not be entered into the online database. The data from every site shall be stored at a single secure server, and different sites shall not be able to access each other's data sheets until the end of the study. A chart that has been entered should be "marked" in a manner that is HIPAA compliant, to avoid duplication of chart reviews.

COTS-I patients will be identified by the Site ID and coded Patient ID. Site ID is unique to all participating hospitals and will correspond the hospital the patient was reviewed at for the Initial Presentation. The coded Patient ID will be taken as the last 5 characters of the patients' National Identification number. For example, a patient with Identification number of "S9230202C," will have a COTS-1 Patient ID of "0202C". Please direct any

uncertainties regarding this to Dr Dinesh Gunasekeran, he can be contacted via email at dineshvg@hotmail.sg.

COTS-I cognito based web-form:

https://www.cognitoforms.com/TTSH/COTS1Form

ENTERING DATA FROM MEDICAL RECORDS

IMPORTANT: Before entering data on a patient at initial presentation, please confirm that the patient is eligible for this study, based on the eligibility criteria detailed above.

General Rules for Entering Data from Chart Reviews:

Procedure for Data entry:

- You will find that the online COTS-I form is intuitive and user friendly.
- Please enter information according to the questions presented to you by the form, which are self explanatory.
- If information necessary to answer a prompted question is not available to you, please select "Unknown".
- The COTS-I form is comprehensive to provide the necessary data for high quality publications. However, it has been programmed as a smart form and tested in

several rounds of trial runs in order to minimize unnecessary data entry. As such it has been optimized to change the questions presented to the user based on his replies to earlier questions.

- For instance, if for "Laterality – Eye Involvement" you select "OD (Right eye)", you will not be prompted to enter data for the OS (Left eye). Similarly, if for "OD Uveitis – Anatomical classification" you select "Anterior", you will not be prompted to enter data relevant for Posterior Uveitis, including "Disc Hyperemia", "Macular edema", "Retinal Vasculitis", etc which are not caused by/ relevant to Anterior Uveitis.
- Please bear in mind that once a form is submitted, the data will be saved in a remote and secure location, and cannot be re-accessed by the COTS-I form.
- As such please "Save" in any situation of uncertain or incomplete data entry.
- Refer to the next section for the procedure for any data entry errors/changes.

Errors/ Interruptions to Data entry/ Save & Resume function

- The form allows you to save progress and resume data entry at a later time.
- Simply click the "Save" button at the bottom of the current page to do so.
- You will be prompted to enter an email, to which a unique link to resume the current form will be sent.
- Please check the Site ID and Patient ID before you resume entering data into the form, in order to minimize errors/ prevent entering data into the wrong form.
- Please bear in mind that once a form is submitted, the data will be saved in a remote and secure location, and cannot be re-accessed by the COTS-I form.
- As such please "Save" in any situation of uncertain or incomplete data entry.

- In the event that you should need to edit the data in a submitted form, please inform the data administrator Dr Dinesh Gunasekeran at dineshvg@hotmail.sg, and then re-enter the data for the patient in an entirely new COTS-I form. He will strike off the incorrect form in order to avoid data entry errors.

Procedure for entering dates:

- Dates are entered using the virtual calendars embedded with the relevant questions on the COTS-I form. Be sure to check the year on the calendar before selecting the month and day.
- If only the year is known based on medical record, please enter the date as 1st of January for that year i.e. for "diagnosed in 2011" the date will be "01/01/2011".
- If only a range of years is known based on medical record, please enter the date as the midpoint i.e. for "diagnosed in 2007-2008" the date will be "01/01/2008". The same applies for wider ranges of years i.e. for "diagnosed in 2007-2011" the date will be "01/07/2009".
- If only the month is known, enter date as the first of that month i.e. for "diagnosed in May 2011" the date will be "01/05/2011".
- If the date, month, and year are all not available, please enter date as 11/11/1111. Do this also for patients with unknown Date of Birth.

Procedure for entering Visual Acuity

- Please select from the options in the drop-down menu provided

- Do not distinguish between Counting Fingers/ Hand Motion at >3feet, <3feet, or "Close to Face" (CFCF or HMCF). These will be noted as Counting Fingers (CF) or Hand Motion (HM) respectively.

Procedure for entering Clinical Findings

- For "AC Inflammation-score (SUN Grading)" please select your answer based on the Standardization of Uveitis Nomenclature (SUN) Working Group grading for intra-ocular inflammation.
- For the Initial Presentation/ 3 Month follow-up, the chronicity of Uveitis may not yet be clear. Please select "Acute (<6 weeks)" if there is no evidence in the charts to suggest illness of longer duration.
- For "Uveitis Severity – Bio-score (SUN Grading)" please select your answer based on the Standardization of Uveitis Nomenclature (SUN) terminology for activity of uveitis.
- For "Phenotypic Diagnoses – Type of Choroiditis", if chart review yields "Non-Serpiginous Choroiditis" without further elaboration with regards to the type, please select the option "Other" and enter "Non-Serpiginous Choroiditis".
- If there is no view of the posterior chamber/ retina for whatever reason (eg dense cataract) please select the "Unknown" option.
- For any information that is not available in chart review, select "Unknown".

Procedure for submitting clinical photos

- This will be prompted by the COTS-I form at every clinical visit
- If available, please upload the photo in **.jpeg or .jpg formats (don't upload .tiff photos due to the heavy image size)**

- If you are able to, adding a description in the open-ended section below the photo on the clinical findings imaged will be of great use.

Procedure for entering Medications – including Anti-Tubercular Therapy (ATT)

- When entering medications, please use the Generic names (and not Brand names).
- When entering medications, please include Name, Dose, and Frequency.
- For eye drops, please include the Concentration. If the eyes are receiving different doses of a medication (or if one eye is not receiving the medication) - please indicate clearly the dose(s), concentration(s), and frequency for each eye.

Procedure for entering Treatment Outcomes

- "Positive response" is defined as two grades improvement in inflammation or healing of choroiditis or vasculitis (as detailed in the form).
- "Negative response" has multiple definitions in this study, as detailed in the form. These are;
  - Patient on ATT with inability to taper oral corticosteroids to <10mg/ day
  - Patient on ATT with inability to taper topical steroids to <2/day
  - Patient on ATT with inability to stop the steroid-sparing immunosuppressive agent
  - Patient on ATT with persistence/ recurrence of inflammation within 6months of completing ATT
  - Patient NOT on ATT with inability to taper medications to the same levels of systemic and topical use at the same follow up duration as the ATT treated group.

- Please do not select “Patient on ATT with persistence/ recurrence of inflammation within 6months of completing ATT” for patients who have not completed at least 6 months of follow-up since ATT was started.

Annexure 1: COTS I Study protocol

Authors for COTS-I handbook:

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