Evaluating a Deep Learning Algorithm in the Diagnosis of Retinopathy of Prematurity (ROP) in Nepal and a prediction model for development of ROP.

Prepared by Nepal Team:

Names: Dr. Srijana Basnet

Edited by: Eli Pradhan

Signature: _____ Date: _____

Reviewed and Approved by:	
Name: Dr. Aeesha Mallik Designation: Principal Investigator Signature: _____	Date: _____

Revision History:

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1				
2				

Protocol No.
Version 1, dated 18th Sept 2024

Project Title: Evaluating a Deep Learning Algorithm in the Diagnosis of Retinopathy of Prematurity (ROP) in Nepal
Clinical Operations Manual
SOP No – AI ROP

Prime Contract

London school of Hygiene and Tropical Medicine (LSHTM)

Funded by

Velux Stiftung

Collaborator

Nepal Netra Jyoti Sangh

Principal Investigator

Sailesh Mishra (NNJS, Nepal)
Srijana Basnet (TUTH, Nepal)
Aeesha Malik (LSHTM, London, UK)

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General Information

Study title: Evaluating a Deep Learning Algorithm in the Diagnosis of Retinopathy of Prematurity (ROP) in Nepal and a prediction model for development of ROP.

NHRC Protocol registration number: 548_2024

Trial registration number: XXXXX

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Date and version number: Version 02, 24th November 2024

Chief Investigator: Aeesha Malik

Sponsor: London School of Hygiene and Tropical Medicine (LSHTM)

Funder: VELUX Stiftung

Compliance: The project will be conducted in compliance with the protocol, ICH GCP

Guidelines and other regulatory requirements applying in the countries in which the trial will be conducted.

Confidentiality: This document contains confidential information that must not be disclosed to anyone other than the Sponsor, the Investigator Team, host organization, and members of the Research Ethics Committee, unless authorized do so.

Conflict interests: We declare no conflict of interests.

Chief Investigator signature:

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Abbreviations

AI:	Artificial Intelligence
AUC:	Area Under the receiver operating Curve
FOV:	Field of View
KMC:	Kathmandu Medical College
LMIC:	Low- and Middle-Income Countries
NICU:	Neonatal Intensive Care Units
NNJS:	Nepal Netra Jyoti Sangh
RE-ROP:	Referral- Warranted ROP
ROP:	Retinopathy of Prematurity
TIO:	Tilganga Institute of Ophthalmology
TR-ROP:	Treatment Warranted ROP
TUTH:	Tribhuvan University Teaching Hospital
VSS:	Vascular Severity Score

1. Main Project Contacts

Chief Investigator
Aeesha Malik *Affiliation:* London School of Hygiene & Tropical Medicine *Address:* Keppel Street, London, WC1E 7HT, United Kingdom *Telephone*: +44 207 927 2577 / +263 772 165 755 *Email*: aeesha.malik@lshtm.ac.uk
Project Management/ PI from Nepal
Project head- Dr. Sailesh Kumar Mishra *Affiliation:* Nepal Netra Jyoti Sangh (NNJS) *Address***:** Tripureswor, *Telephone*: +9779841241014 *Email:* smishra@nnjs.org.np **Research Manager- Ranjan Shah** *Affiliation:* Nepal Netra Jyoti Sangh (NNJS) *Address***:** Tripureswor, *Telephone*: +9779845325650 *Email:* ranjan_shah@nnjs.org.np **Dr Srijana Basnet-PI from Nepal** *Affiliation:* Tribhuvan University Teaching Hospital (TUTH) *Address:* TUTH *Telephone*: *Email:* **Name: Dr Eli Pradhan PI from Nepal** *Affiliation: Tilganga Institute of Ophthalmology (TIO)* *Email: eli.pradhan@tilganga.org*

Phone: +977 9818517960

Site Contact

Name: Research assistant or ROP research coordinator or officer? (To be advertised)

Affiliation:

Address:

Telephone:

Email:

For

Name:

Address: London School of Hygiene and Tropical Medicine

Address: Research Governance and Integrity Office, Keppel Street, London WC1E 7HT, UK

Email:

Study Statistician

Name:

Affiliation: London School of Hygiene & Tropical Medicine

Address: Keppel Street, London, WC1E 7HT, United Kingdom

Telephone: +44 207 927 2577

Email:

Name: Manish Paudel

Affiliation : *Tilganga Institute of Ophthalmology (TIO)*

Email:

Phone:

Co-investigators

Name: Dr Sabina Shrestha
Affiliation: Kathmandu Medical College (KMC)
*Email:*sabina.drs2021@gmail.com
Phone:+9779841287373

Name: Dr Pratap Karki
Affiliation: Tribhuvan University Teaching Hospital (TUTH)
*Email:*karkipratap@gmail.com
Phone:+9779841526860

Name: Dr Priyanka Shrestha
Affiliation: Kathmandu Medical College (KMC)
Email:
Phone:

Name: Dr Srijana Adhikary
Affiliation: Tilganga Institute of Ophthalmology (TIO)
Email:
Phone:

Name: Dr Suman Raja Manandhar
Affiliation: *Kathmandu Medical College (KMC)*
Email:
Phone no:

Data management/ Cleaning

Name:
Affiliation: London School of Hygiene & Tropical Medicine

Address: Keppel Street, London, WC1E 7HT, United Kingdom

Telephone: +44 207 927 2577
Email:

Name: Pradeep Banjara

Address: Tilganga Institute of Ophthalmology (TIO)

Email:

Phone:

Name: Pratibha Neupane
Affiliation: ***Tilganga Institute of Ophthalmology (TIO)***

Address:
Telephone:
Email:

Experts

External Expert:

Name: Dr Peter Campbell

Address:

Email:

Phone:

INTERNAL EXPERT

Name: Dr Richard Brown

Affiliation: London School of Hygiene & Tropical Medicine

Address: Keppel Street, London, WC1E 7HT, United Kingdom

Telephone: +44 207 927 2577

Email:

2. Executive Summary

Retinopathy of prematurity (ROP) is a potentially blinding disease of the infants born preterm and has been recognized as the fifth leading cause of childhood blindness in postindustrial and developed nations by World Health Organization's Vision 2020 programme. Three phases of ROP epidemics have been observed worldwide since this disease was first described and Nepal is currently facing the third epidemic with improved neonatal intensive care and survival of the preterm children. The neonatal mortality rate in Nepal has significantly decreased from 27.998 per 1000 live births to 16.998 per 1000 live births over the last decade (UNICEF data) (Gilbert et al., 2001). Each year, globally, about 32,300 babies are substantially affected by ROP out of which around 20,000 results in severe visual impairment or blindness (Hong et al., 2022).

In Nepal, the incidence of ROP has been recorded as 22-30%. Among these, 3.2% had severe stages of ROP requiring intervention. Recently, due to financial, social and medical progress there has been expansion of the neonatal services in our country leading to an increase in neonatal survival. Thus, we can see an increase in the prevalence of ROP across various parts of the country. Multiple studies in different centers concluded significant risk factors of developing ROP as oxygen supplementation, low birth weight, low gestational age and sepsis (Adhikari et al., 2008) (Shrestha et al., 2010) (Yadav et al., 2020).

The aim of this prospective cohort study is to evaluate the efficacy of artificial intelligence (AI) based on deep learning algorithm (i-ROP) developed from wide field digital images for the diagnosis of ROP. We proposed to compare the diagnostic accuracy of AI for ROP with the Reference standard diagnosis made by human readers for different severities of ROP. The secondary objectives will be to measure diagnostic accuracy of different grades of Vascular severity score (VSS) given by AI for prediction of Referral warranted (RW-ROP) and Treatment requiring (TR ROP). The study also aims to develop a prediction model for development of ROP based on clinical characteristics. The study will be conducted over the period of 3 years with total number of enrolled babies to be 584. The recruitments for this multicenter study will take place in 3 hospitals in Kathmandu, Nepal. The participants will be followed up at 1-2 weekly intervals until 42 weeks or retinal vascularization is complete. We also plan to evaluate the performance of a new, simple and cost-effective smartphone-based diagnostic tool for ROP in a later phase.

If the results of this study are consistent with an earlier study, then it will offer important insights into the potential of AI systems as a reliable, cost-effective alternative for detection ROP and might reduce burden on specialists. It also helps in expansion of ROP screening, enhances decision-making and improves overall outcomes for premature infants at risk of ROP.

3. Synopsis

Project Title	**Evaluating a Deep Learning Algorithm in the Diagnosis of Retinopathy of Prematurity (ROP) in Nepal and a prediction model for development of ROP.**	
Internal ref. no. (or short title)	AI-ROP	
Study Design	Prospective Cohort study	
Study Participants	Premature babies Less than 34 weeks: PMA and Birth weight less than 2000 gm	
Planned Sample Size	584	
Intervention		
Study Visits	**Intervention** **Outcome ascertainment**	
Planned study Period	January 2025 – December 2028	
	Objectives	**Outcome Measures/Endpoints**
Primary study outcome	Evaluate the efficacy of artificial intelligence (AI) based on deep learning algorithm (i-ROP) developed from wide field digital images for the diagnosis of ROP. Compare the diagnostic accuracy of AI for ROP with the Reference standard diagnosis made by human readers for different severities of ROP.	Screening of premature babies, less than 34 weeks PMA and less than 2000 gm. Images taken sent to the graders and analysis Comparison with I-ROP
Secondary study outcomes	Measure diagnostic accuracy of different grades of Vascular severity score (VSS) given by AI for prediction of Referral warranted (RW-ROP) and Treatment requiring (TR ROP). The study also aims to develop a prediction model for development of ROP based on clinical characteristics.	Diagnosis of RW-ROP and TR ROP.

	In the second phase: Evaluate the performance of a new, simple and cost-effective smartphone-based diagnostic tool for ROP.	

4. Introduction

This collaborative multicenter academic clinical study is funded from Velux Stiftung Research Grant will be executed by Nepal by Nepal Netra Jyoti Sangh (NNJS) in collaboration with London school of Hygiene and Tropical Medicine (LSHTM). For the implementation of the study, a separate agreement has been signed between NNJS and LSHTM (on …. Dated))

The aim of this prospective cohort study is to evaluate the efficacy of artificial intelligence (AI) based on deep learning algorithm (i-ROP) developed from wide field digital images for the diagnosis of ROP. We proposed to compare the diagnostic accuracy of AI for ROP with the Reference standard diagnosis made by human readers for different severities of ROP. The secondary objectives will be to measure diagnostic accuracy of different grades of Vascular severity score (VSS) given by AI for prediction of Referral warranted (RW-ROP) and Treatment requiring (TR ROP). The study also aims to develop a prediction model for development of ROP based on clinical characteristics. The study will be conducted over the period of 3 years. The recruitments for this multicenter study will take place in 3 hospitals in Kathmandu, Nepal. The participants will be followed up at 1-2 weekly intervals until 42 weeks or retinal vascularization is complete. We also plan to evaluate the performance of a new, simple and cost-effective smartphone-based diagnostic tool for ROP in a later phase. If the results of this study are consistent with an earlier study, then it will offer important insights into the potential of AI systems as a reliable, cost-effective alternative for detection ROP and might reduce burden on specialists. It also helps in expansion of ROP screening, enhances decision-making and improves overall outcomes for premature infants at risk of ROP.

5. Purpose

This SOP has been developed to ensure uniform guidelines for participant recruitment from NICU/ Ophthalmology OPD (first contact area), data collection on risk factors for ROP, image acquisition, follow-up of enrolled infants, reporting of retinal images by Human readers, AI algorithm diagnosis and statistical analysis. It identifies the safety and quality control measures that have to be adopted for all procedures to prevent accidents, improve efficiency and accuracy.

6. Scope

This SOP applies to research officers, ophthalmic assistants and site investigators who will be involved in the study activities and their Quality Control (QC) at the site.

3.1 ***Study hospital sites in Nepal:***

1. Tribhuvan University Teaching Hospital (TUTH) and B.P Koirala Lions club of Ophthalmic center (BPKLOCS)
2. Kathmandu Medical College (KMC)
3. Tilganga Institute of Ophthalmology (TIO)

Coordinating Investigator: The investigator who has the responsibility to coordinate between the different investigators involved in a study at one site or different sites in case of a multi-centre study. Dr Sailesh Kumar Mishra from NNJS and Dr Srijana Basnet from TUTH are the Coordinating investigators for this study.

Documentation: All records (including written documents, electronic, retinal image, patient medical record etc.) that describe or record the methods, conduct and results of the study, and the actions taken. The Documents include Protocol, copies of submissions and approvals from ethics committee, investigator(s)' particulars, informed consent documents, monitor reports, audit certificates, relevant letters, reference ranges, raw data, completed CRFs and the final report.

Institutional Ethics Committee (IEC): An independent review board or committee (Nepal Health Research Council) comprising of medical/ scientific and non-medical/ non-scientific members, whose responsibility is to verify the protection of the rights, safety and well-being of human subjects/ participants involved in a study. The independent review provides public reassurance by objectively, independently and impartially reviewing and approving the "Protocol" the suitability of the investigator(s), facilities, methods and material to be used for obtaining and documenting "Informed Consent" of the study participants and adequacy of confidentiality safeguards. The study has been granted Ethical Clearance from NHRC.

Good Clinical Practice (GCP): It is a standard for clinical studies or trials that encompasses the design, conduct, monitoring, termination, audit, analyses, reporting and documentation of the

studies. It ensures that the studies are implemented and reported in such a manner that there is public assurance that the data are credible, accurate and that the rights, integrity and confidentiality of the subjects/ participants are protected. GCP aims to ensure that the studies are scientifically authentic and that the clinical properties of the "Investigational Product" are properly documented. All investigators have completed GCP certification before the start of the project.

Investigator: A person responsible for the conduct of the study at the different sites. Investigator is responsible for the rights, health and welfare of the study subjects/ participants. In case the study is conducted by a team of investigators at the study site then the designated leader of the team should be the Principal Investigator.

For the purpose of this academic multicenter study, the PI and Co-PIs are from TIO, IOM, KMC (Nepal) and LCTMH London. Within each hospital we have co-investigators/ site investigators and the leader of the team of investigators at the sites is the lead site investigator.

Roles and Responsibilities

PI: Aeesha Mallik, Sailesh Kumar Mishra, Srijana Basnet

Principal Investigator is the person responsible for overseeing the research project.

1. Leads the clinical research team and, along with the other members of the research team,
2. Regularly monitors study participants' health to determine the study's safety and effectiveness.
3. Responsible for the preparation, conduct, and administration of a research grant, cooperative agreement, or other sponsored project in compliance with applicable laws and regulations and institutional policy governing the conduct of clinical research
4. Review, prepare, and submit results for publication and register publication, as required by sponsor
5. Monitor expenditures regularly to ensure that funds are managed in compliance with sponsor terms and conditions and only expended to directly support and benefit the project
6. Ensure the accurate and timely submission of all required reports throughout the life of the award
7. Ensure appropriate training of project staff

8. Report any incidents that occurred during the performance of research activities that resulted in or could have led to injury or damage to property

Co-PIs have responsibilities similar to that of a PI on research projects.

Sabina Shrestha: as Co_PI from KMC, screening, guiding the research staffs
Priyanka, , screening, guiding the research staffs and will be grader from KMC
Srijana Basnet: Main PI of the study, proposal writing, SOP formulation, support Dr Pratap
Dr Pratap: Screening, grading, treatment among ROP babies
Dr Eli Pradhan: PhD candidate, screening, treatment, coordination of all three centres,
Ranjan Shah: Proposal writing, coordination of all PI and Co_PIs

All will be involved in scientific paper writing

Manish Paudel and Pratibha Giri will be involved in statistical analysis, data collections and data management
Pradeep Banjara: Data Management and data cleaning
Garima Paudel, Rusha Karki, Kumar Rai and Reshma Prajapti from KMC: Screening, data collections in forus camera

Role and Responsibilities of the Study Assistant (SA):
Three SA with Diploma degree in medicine/Nursing will be recruited before the initiation of the study

1. **Participant Screening and Recruitment:**
    - Screen all newborns admitted to the hospital or visiting the OPD to identify those meeting the study's inclusion criteria.
    - Ensure proper documentation of eligibility and record relevant medical details.
2. **Coordination and Scheduling:**
    - Coordinate with the NICU, treating physicians, and ophthalmology departments to ensure timely fundal examinations and imaging for study participants.
    - Arrange follow-up visits and ensure participants adhere to the scheduled examinations.

3. **Data Collection and Management:**
    - Collect baseline medical information and clinical details from hospital records or discharge summaries.
    - Enter data accurately into screening and follow-up forms, ensuring completeness and compliance with the study protocol.
4. **Fundal Imaging Support:**
    - Assist in organizing fundal imaging sessions before discharge or during follow-up visits.
    - Ensure retinal images are uploaded to the designated server for AI algorithm analysis.
5. **Communication and Consent:**
    - Explain the study process to parents or guardians and obtain informed consent before enrolling newborns.
    - Provide necessary instructions to families regarding follow-up visits or procedures.
6. **Quality Assurance:**
    - Monitor adherence to clinical operating guidelines for ROP screening.
    - Ensure consistent implementation of study protocols across all sites.
7. **Reporting and Documentation:**
    - Regularly report to the study coordinator on the progress and challenges encountered.
    - Maintain organized records for all participants, ensuring data confidentiality and integrity.
8. **Site-Specific Duties:**
    - Stationed full-time at the assigned hospital site, the SA serves as the point of contact for the study at that location.
    - Collaborate with hospital staff to integrate study activities seamlessly with routine clinical care.

Ophthalmic Assistants

TIO: Ms Rusha Karki, Kumar Rai (Eye Workers): 1 camera

BPKLCOS: Garima Paudyal, need 1 more (Optometrist)

KMC: Reshma Prajapati (Optometrist)

Role and Responsibilities of the Ophthalmic Assistant (OA):

1. **Fundal Imaging and Examination:**
    - Conduct fundal imaging of newborns enrolled in the study using the designated wide-field digital imaging (WFDI) system.
    - Ensure high-quality retinal images are captured for accurate analysis and interpretation.
2. **Screening and Diagnosis Support:**
    - Collaborate with the research team and treating physicians to ensure timely detection and documentation of ROP.
3. **Coordination with Study Team:**
    - Work closely with the Study Assistant (SA) to ensure that fundal imaging is conducted for eligible newborns before discharge or during follow-up visits.
    - Coordinate with the study team to verify imaging schedules and meet study timelines.
4. **Data Management:**
    - Upload retinal images to the designated server for review and AI-based analysis.
    - Maintain organized records of all imaging data, ensuring accuracy and confidentiality.
5. **Technical Maintenance and Troubleshooting:**
    - Ensure the proper functioning of imaging equipment, including regular maintenance and troubleshooting as needed.
    - Report any technical issues with the imaging system to the study coordinator promptly.
6. **Family and Participant Interaction:**
    - Provide clear instructions and reassurance to parents/guardians during fundal imaging procedures to ensure cooperation.

- Address any concerns raised by families related to the imaging process or follow-up visits.

7. **Compliance and Safety:**
    - Adhere to clinical operating guidelines for fundal imaging and ensure all procedures are performed safely and effectively.
    - Follow infection control measures and ensure the comfort of newborns during imaging sessions.
8. **Quality Assurance:**
    - Review captured images for clarity and ensure they meet the required standards for analysis.
    - Re-capture images if necessary to maintain consistency in data quality.
9. **Reporting:**
    - Provide regular updates to the study coordinator on imaging progress and any challenges encountered.
    - Document all imaging sessions, including any observations made during the procedure.
10. **Site-Specific Duties:**

- Be available at the assigned hospital site full-time to ensure smooth execution of imaging tasks.
- Collaborate with hospital staff to integrate study imaging activities into routine clinical care.

CO-PI:

KMC- Sabina Shrestha, Priyanka Shrestha,

TUTH- Pratap Karki

TIO- Eli Pradhan, Srijana Adhikari

Role and Responsibilities of the Site Co-Principal Investigator (Co-PI):

1. **Study Oversight and Coordination:**
    - Oversee the implementation of the study at the assigned site, ensuring adherence to the protocol and research objectives.
    - Act as the primary point of contact between the study team and the hospital administration for site-specific matters.
2. **Ethical Compliance:**
    - Ensure that all study activities comply with ethical guidelines and institutional review board (IRB) approvals.
    - Monitor the informed consent process to ensure that participants and their families are fully informed about the study.
3. **Participant Recruitment and Screening:**
    - Supervise the recruitment and screening of eligible participants, ensuring that inclusion and exclusion criteria are strictly followed.
    - Address any challenges encountered during recruitment and propose solutions to ensure the study's progress.
4. **Clinical and Technical Supervision:**
    - Oversee the performance of clinical procedures such as fundal imaging and medical record reviews.
    - Ensure that all imaging and diagnostic activities align with clinical operating guidelines for ROP.
5. **Image Reading**
    - Drs Eli, Pratap and Priyanka will also serve as human grader for the study. They will independently read the image and classify image according to ICROP-3 classification
6. **Data Quality Assurance:**
    - Monitor the collection, entry, and management of study data to maintain accuracy, consistency, and confidentiality.
    - Review data periodically to identify and resolve any discrepancies or gaps in documentation.
7. **Team Supervision and Support:**

- Supervise the work of Study Assistants (SAs), Ophthalmic Assistants (OAs), and other team members at the site.
- Provide guidance and training to ensure all staff understand their roles and responsibilities.

8. **Communication and Reporting:**
    - Maintain regular communication with the Principal Investigator (PI) and other site Co-PIs to provide updates on study progress and challenges.
    - Submit site-specific progress reports and participate in periodic review meetings.
9. **Problem-Solving and Risk Management:**
    - Address operational issues at the site, such as delays in imaging, technical challenges, or participant retention problems.
    - Develop strategies to mitigate risks and ensure smooth execution of study activities.
10. **Collaboration:**
    - Work closely with hospital staff, including NICU teams, ophthalmology departments, and administrative units, to integrate study activities into routine hospital workflows.
    - Facilitate collaboration between research staff and healthcare providers for optimal study implementation.

11. **Publication and Dissemination:**
    - Work with PI in report dissemination and paper writing

Flow chart: In Appendices

All steps for 3 different hospitals

Baby consented

Data collections part, calling, data collections, from hospital records,
Hospital coordinator, 1 for each hospital: photographs, completion of data entry,

Role and responsibility of NNJS Co-PI/ Research Manager AI-ROP (Ranjan Shah)

1. **Financial Management:**
    - Oversee, process, and monitor all financial transactions in the research portfolio, including sponsor and cost-sharing funds where applicable.
2. **Project Scope and Budget Management:**
    - Collaborate with the Principal Investigator (PI) to review and revise project scope, budgets, or changes in effort. Submit necessary change requests to Sponsored Research.
3. **Research Records Maintenance:**
    - Assist the PI in keeping research records up to date, including IRB submissions, regulatory records, study data, and consent forms, in a timely manner.
4. **Site Visits and Data Management:**
    - Conduct periodic visits to research centers to monitor and manage data collection and ensure compliance with protocols.
5. **Data Maintenance and Storage:**
    - Maintain patient-specific and center-specific data, ensuring all information is securely stored on cloud platforms.

Role and Responsibilities of the Principal Investigator (PI)

1. **Leadership and Oversight:**
    - Provide overall leadership for the research project and ensure all activities align with the study objectives and protocols.

2. **Protocol Development and Adherence:**
    - Develop and finalize the study protocol, ensuring compliance with ethical standards, institutional guidelines, and sponsor requirements.
    - Ensure all study personnel strictly adhere to the approved protocols.
3. **Regulatory Compliance:**
    - Oversee all regulatory submissions, including IRB approvals and amendments, and ensure timely updates of required documentation.
4. **Team Management:**
    - Supervise and provide guidance to the research team, including co-investigators, study assistants, and site staff.
    - Facilitate communication between team members and stakeholders to ensure smooth project execution.
5. **Data Integrity and Quality Control:**
    - Ensure accurate and timely data collection, entry, and analysis.
    - Monitor the quality and integrity of study data throughout the project.
6. **Financial Oversight:**
    - Manage project budgets and financial transactions in collaboration with the site co-investigators and financial administrators.
7. **Participant Recruitment and Safety:**
    - Ensure proper recruitment, screening, and consent of study participants.
    - Prioritize the safety and well-being of participants by monitoring adverse events and taking appropriate actions when needed.
8. **Monitoring and Reporting:**
    - Conduct regular site visits to monitor progress and address challenges.
    - Prepare and submit progress reports to funding agencies, sponsors, and ethics committees as required.
9. **Publication and Dissemination:**
    - Analyze study results and ensure timely publication in peer-reviewed journals.
    - Share findings with stakeholders to maximize the study's impact on clinical practice and policy.
10. **Problem-Solving:**

Address and resolve any challenges or obstacles encountered during the study

DSMB board:

1. Responsible for providing their expert opinion in cases of Serious adverse events
2. Non biased judgment to be provided

Members

1. Dr Suchita Joshi (Already consented)
2. Dr Salma KC Rai (Needs consent)
3. Needs Lawyer
4. Needs NHRC

Serious Adverse Event (SAE): An AE or ADR that is associated with death, inpatient hospitalisation (in case the study was being conducted on out-patients), prolongation of hospitalisation (in case the study was being conducted on in-patients), persistent or significant disability or incapacity, a congenital anomaly or birth defect, or is otherwise life threatening.

Source Data: Original documents (or their verified and certified copies) necessary for evaluation of the clinical trial. These documents may include Study Subjects' files, recordings from automated instruments, tracings, X-Ray and other films, laboratory notes, photographic negatives, magnetic media, hospital records, clinical and office charts, Subjects' diaries, evaluation check-lists, and pharmacy dispensing records.

Sponsor: An individual or a company or an institution that takes the responsibility for the initiation, management and/ or financing of a clinical study. An Investigator who independently initiates and takes full responsibility for a trial automatically assumes the role of a Sponsor, This study had sponsor as LSTMH

And Locally is by NNJS

Standard Operating Procedures (SOP): Standard elaborate written instructions to achieve uniformity of performance in the management of clinical studies. SOPs provide a general framework for the efficient implementation and performance of all the functions and activities related to a particular study.

Study subject/participant: An individual participating in a clinical trial as a recipient of the Investigational Product. A study participant may be a healthy person volunteering in a trial or a person with a medical condition that is unrelated to the use of the Investigational Product or a person whose medical condition is relevant to the use of the Investigational Product.

Note: All definitions have been taken from the Indian GCP guidelines by CDSCO except for DSMB, which has been taken from ICH-GCP

5. Procedure

5.1 Study sites:

Study hospital sites:

1. NICU/ Neonatal and pediatric wards of Tribhuvan University Teaching Hospital (TUTH) and B.P Koirala Lions club of Ophthalmic center (BPKLOC) of Institute of Medicine (IOM)
2. NICU/ Neonatal and pediatric wards of Kathmandu Medical College (KMC)
3. OPD of Tilganga Institute of Ophthalmology (TIO)

This prospective cohort study will be done from the NICU/ Neonatal and pediatric wards KMC and TUTH and follow-up will be done in Ophthalmology OPD of TIO and BPKLOC.

The hospital site departments of pediatrics/ Ophthalmology and administration will identify some dedicated space/ room for the smooth implementation of the study related activities. Similarly, NNJS will identify dedicated room/area, will be the main site for the office bearers of the Project such as Research Officer where all the completed paper documents are safely placed.

5.2 Ethical clearance:

We have obtained ethics approval for conduct of the study from LSTMH, Nepal Health Research Council (NHRC) and the Nepal hospital sites.

***Participants*:**

Instructions for the study study assistantat the hospital site:

Screen all infants admitted at NICU, neonatal unit (NNU), Pediatric ward of TUTH/KMC or coming to OPD for ROP screening.

Header information

Box 1

Header information has to be complete before you start collecting and entering the data.

As soon as user enters his/her user ID and password, a dashboard with all form options will open.

User will select screening form…….

Once it opens he/she will enter a **Screening ID** for the infant who he/she is going to screen.

The first alphabet on the screening number is 'S' which stands for screening.

The second box will have a number denoting the hospital site/ site code.

So for eg: 1=TUTH
2=BPKLOC
3=KMC
4=TIO

The next 4 numbers in the screening ID denote the screening number:

The screening ID for the 1st infant screened at TUTH will be "S1001"

The screening ID for the 1st infant screened at BPKLOC will be "S2001"

The screening ID for the 1st infant screened at KMC will be "S3001"

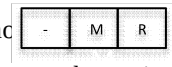
The screening ID for the 1st infant screened at TIO will be "S4001

The first two boxes will auto populate depending on the site where the screening is happening. The study research officer to enter the next four digits denoting the sequential screening number for the site. He/She will start with 001.

Date and time

Once the screening ID has been filled, the current date and time will appear in the header. The date will come in the format of dd/mm/yyyy. The the alphabet time will come in the 24 hour format xx:xx hours.

Participant Initials

Next the study research officer will fill the participant's initials. There are 3 boxes for 3 letters/ characters. The first letter denotes the first of infant's name. If the infant has not been given a name, put a dash for the first letter. The second letter denotes the first alphabet of the mo 

d the third letter denotes the first alphabet of the father's name.

Eg: The infant's has not been given a name, the mother's name is Madhu and the father's name is Ramesh; the Participant Initials will be -/M/R

/

Once header information is complete, the study research officer will screen the infant for eligibility.

5.3 Inclusion criteria

Inclusion criteria for the study is any of the following criteria

a. Gestational age < 34 weeks and/or birth weight < 2000g.
b. Gestational age 34-36 week in children with risk factors such as need of respiratory support, oxygen therapy for more than 6 h, sepsis, episodes of apnea and need of blood transfusion, exchange transfusion or unstable clinical course as determined by pediatrician.

For any babies admitted to ward or coming to OPD, Research officer will **determine the gestational age and record birth weight of the infant**

Determination of gestational age

- Obtain the date of the first day of the mother's last menstrual period (LMP) through patient records or interviews.
- If LMP is uncertain or not recalled, proceed to gestational age estimation by ultrasound (USG).
- From the LMP date, calculate the number of days/weeks that have passed up to the date of birth.

Formula: Gestational Age (weeks)= $\frac{\text{Days since LMP to the date of birth}}{7}$

- The full-term pregnancy is considered to be 40 weeks (280 days) from the LMP.
- If LMP is unavailable or uncertain and/or discrepancies between LMP and clinical findings (as per treating pediatrician), calculate gestational age by early USG dating.
- Early USG dating is any of the first-trimester ultrasound (before 13 weeks of gestation) which should be used as the primary method for estimating gestational age. If the difference between the GA by LMP and first-trimester USG is more than 7 days, the USG result should be considered more accurate for dating so document gestational age based on early USG dating.

- If LMP is unavailable or uncertain and/or discrepancies between LMP and clinical findings (as per treating pediatrician) and early USG dating unavailable, document gestational age based on modified ballard scoring done by treating pediatrician.

The infant fulfills eligibility criteria if he/she if <34weeks and/or birth weight<2kg

<u>For infant between 34-36 weeks, look for clinical course of an infant</u>

a) cardio-respiratory instability **AND/OR**

b) prolonged oxygen therapy **AND/OR**

c)repeated episodes of apnoea of prematurity **AND/OR**

d) anaemia needing blood transfusion **AND/OR**

e) neonatal sepsis **AND/OR**

f) believed by their attending pediatrician or neonatologist to be at high risk.

Definition

Cardio-respiratory instability

A newborn is considered as having cardio-respiratory instability if he/she requires respiratory or circulatory support. Respiratory support includes invasive or non-invasive ventilation support, such as continuous positive airway pressure, high-flow nasal cannula oxygen therapy and non-invasive positive pressure ventilation. The circulatory support includes volume expansion, and vasoactive or positive inotropic drugs.

Prolonged oxygen therapy

Newborns require more than 6hours of supplemental oxygen therapy.

Repeated episodes of apnoea of prematurity

Apnea of prematurity is defined as a sudden cessation of breathing that lasts for at least 20 seconds or is accompanied by bradycardia or oxygen desaturation (cyanosis) in an infant younger than 37 weeks gestational age.

- Bradycardia in a premature neonate is considered clinically significant when the heart rate slows by least 30 bpm from the resting heart rate.
- An O_2 saturation level of less than 85% is considered pathologic in this age group, as is a decrease in O_2 saturation should it persist for 5 seconds or longer.
- Repeated apnea is defined as repeated (over three) episodes of apnea after the first hour of age.

Anaemia needing blood transfusion

Any newborn who requires Packed cell transfusion for anemia

Sepsis

Newborn with suspected or confirmed sepsis

Irrespective of the clinical course, a newborn is considered eligible for screening for ROP if attending pediatrician or neonatologist believe to be at high risk.

Screening age of newborn for the first retinal examination

- All babies meeting the inclusion criteria will be screened for ROP by fundal examination within 30 days of life.
- For babies born <28 weeks and <1200g will be screened earlier within 20 days of life.
- If any babies meeting the inclusion criteria is planned for discharge before the first examination for ROP, fundal examination will be done irrespective of their chronological age.

Enrollment Process

. Three study assistants, one assigned to each site, will be recruited prior to the start of the study. These assistants will be employed full-time for the duration of the study, with one stationed at each hospital location.

He/she will visit the NICU at KMC or TUTH everyday to screen all newly admitted infants. SA will evaluate whether each newborn meets the birth weight, gestational age, or other inclusion criteria. After assessing eligibility, he/she will consult with the treating doctor, co-investigator or review hospital records to identify any risk factors contributing to the development of ROP and record this information on the screening form (SF). It is also SA's responsibility to determine if the newborn has reached the appropriate age for the first ROP screening and notify the ophthalmic assistant for fundal imaging.

SA will be responsible for informing the family about the study and obtained consent for participation of their newborn babies in the study.

If a newborn meeting the study's inclusion criteria is being discharged, the SA ensures that a fundal examination is either performed before discharge or that the family is advised to bring the baby to the Ophthalmic OPD of the designated hospital for fundal imaging.

The study assistant will also screen infants visiting the OPD for eye evaluations to check for eligibility based on the inclusion criteria. After confirming eligibility, they will review hospital documents or discharge summaries to identify any risk factors for the development of ROP, recording this information on the screening form (SF). They will also verify that the infant has reached the appropriate age for ROP screening and has not already undergone treatment for ROP. If the infant has been previously treated for ROP, they will be excluded from the study.

For newborns already enrolled in the study and returning for follow-up examinations in OPD, the study assistant ensures that all relevant medical details are collected and accurately recorded in the study follow-up form. They also inform OA for fundal imaging.

5.4 Obtaining the Informed Consent

If the infant fulfills the inclusion criteria, has no exclusion and has reached the age for first screening for ROP and is found to be eligible for the study, SA will take the parents /family member of the eligible newborn to the separate dedicated room where he/she will provide them an information about the study and take written informed consent for participation in the study from the parent (s)/ caregiver of the eligible infant. The SA will then give one copy of the signed

informed consent document (ICD) (participant information sheet [PIS] & participant informed consent form [PICF]) to the parent (s)/ caregiver

<u>Note</u>: If the parent(s)/ caregiver says that although they would like their baby to participate in the study they are not from Kathmandu valley and will not be able to come for the follow-up visit or that they have plans to be away from home for a few days in the coming weeks or they might have to leave in case of an emergency, reassure them that they could still participate.

Enrollment and followup visit documentation

The Study Assistant (SA) will securely maintain the record file containing all paper documents at each hospital site, ensuring strict confidentiality. Additionally, the SA will manage the study calendar, recording follow-up visit dates and ensuring timely scheduling and tracking of participant appointments.All Case Report Forms (CRFs) will be completed electronically and securely uploaded to the cloud.

Image Acquisition Process

Equipment:

Forus 3Ntra wide-field digital imaging (WFDI) camera

The **Forus 3Ntra** is a wide-field digital imaging (WFDI) camera designed for capturing high-resolution retinal images. It provides a broad view of the retina, essential for screening and diagnosing conditions in neonates and premature infants. It is simple to use so can be easily operated by optometrists or Ophthalmic assistant after short training course. The process of image acquisition cause minimal discomfort for the infant during imaging. It produces high-quality images that can be analyzed, stored, and shared for diagnostic purposes. Hence, facilitates remote diagnosis and consultations, especially beneficial in under-resourced settings.

The 3Ntra camera is particularly advantageous for use in neonatal intensive care units (NICUs) and for screening programs in developing countries, where early detection and treatment of ROP are crucial.

Image Capture Procedure:

Once the initial data of the infant is registered in the computer,

1. the forus camera is adjusted with foot pedal, lights, and other accessories
2. Baby is kept in the face up position with proper baby wrapping and holding of baby by the support staffs
3. Pediatric speculum is kept in the eye to be examined.
4. With the forus imaging probe, the first few images are captured of the Anterior view of the lids, cornea, Lens.
5. The probe is first kept in the primary position of the baby, followed by all quadrants, such as nasal, superior nasal, superior temporal, temporal, inferior temporal, inferior, inferior nasal and images are captured by adjusting the foot pedal
6. Once one eye is done, it is changed to another eye in computer settings.
7. Similar images are taken in the other eye.
8. For the storing of the images, there are different image storing circles, where the corresponding images are dragged to fill it up.
9. The stored images are then exported to the Cloud for sending it to the Image readers

Instructions to Ophthalmic Assistant officer Fundal imaging.

1. Babies may be screened in various clinical settings like in outpatient departments, pediatric wards and neonatal intensive care unit. Babies will be fed one hour before screening and should be kept warm and covered well using a blanket during screening.

2. Proper aseptic precaution will be taken before every examination
3. Proper written consent to be taken from the parents before proceeding
4. Proper counselling of the procedure with risks explained to them
5. The dilator drops used- their concentration, timing and the number of times it is instilled will be documented in the nursing chart.
6. Pupil dilatation will be done using Tropicamide 0.5-1% and Phenylephrine 2.5%. One drop will be applied two to three times every 10-15 minutes.
7. All babies will have both eye images from the standard Portable WFBI (the Forus) All images will be acquired by a trained Ophthalmic Assistant (OA) who will be trained by experienced person on using this camera systems. This will be followed by a specific training course in the new camera system. The trained clinicians should be equally familiar

with both devices. All pictures however will be seen and diagnosed by an ophthalmologist of the hospital. All findings will be clearly documented.

Image Upload and Storage:

- Images will be uploaded to a secure web-based platform **(iTeleGENx)** where they will be stored anonymously. The platform will facilitate easy access for remote graders and AI training purposes.

Reference standard diagnosis by human grader

Three experienced graders (Dr Eli Pradhan: TIO, Dr Pratap Karki: TUTH, Dr Priyanka Shrestah: KMC)in telemedicine image-based diagnosis will review the anonymized images with ~~2~~ 3 graders assigned to each image from the local research site. Each grader will be presented with patient demographic characteristics, including birth weight and gestational age, and the graders will determine ROP diagnosis, including zone, stage, plus and presence of aggressive ROP for individual eyes according to the International Classification of Retinopathy of Prematurity III (ICROP 3). In cases of disagreement between ~~two~~ three graders a third expert will adjudicate the diagnosis. The final diagnosis made is taken as reference standard diagnosis (RSD) for the particular examination.

i-ROP and DL algorithm

An Artificial intelligence (AI), Imaging and Informatics in ROP (i-ROP) deep learning (DL) algorithm has been developed by the i-ROP Consortium which will be applied to analyze each optic disc-containing image in the datasets.

.For this, WFBI images are data sets will be analyzed by ResNet deep learning architecture which will classify dataset into normal, pre-plus or plus disease . For this all images are exported to the team of Dr Peter Campbell.

Additionally, AI system will also generate vascular severity score (VSS) ranging from 1 to 9 for each images dataset. VSS is a quantitative score for assessing ROP severity by comparing the degree of dilatation and tortuosity visible in WFBI to previously published standard images. VSS will subsequently be used for patient-level predictions of type 0, 1 or 2 ROP {No ROP, Referral warranted (RW-ROP) and Treatment requiring (TR-ROP)}.

Follow-Up Examinations:

- Based on retinal findings, follow-up schedules will be set. Infants showing early signs of ROP will be closely monitored with more frequent examinations. Follow-ups will be managed by research assistants who will track appointments and send reminders to families.
- Follow up calls are to be sent by the research officer

Data and Safety Monitoring Board:(Independent Data Monitoring Committee (IDMC), Monitoring Committee, Data Monitoring Committee): An independent data monitoring committee is established to oversee the safety and integrity of a study, especially clinical trials or research involving human subjects. In this study, the DSMB would play the following roles:

Key Responsibilities:

1. **Monitoring Safety**: Regularly review study data to ensure the safety of participants, particularly in terms of any adverse events related to the screening methods.
2. **Ethical Oversight**: Ensure that the study adheres to ethical standards, protecting the rights and well-being of participants, especially the premature infants involved.
3. **Evaluating Study Progress**: Review interim data to assess whether the study is progressing as expected, and recommend any modifications or early termination if necessary.
4. **Risk-Benefit Assessment**: Regularly evaluate the risk-benefit ratio of continuing the study, ensuring that the benefits of the AI diagnostic tool outweigh any risks.

Board Composition:

The DSMB for this study would ideally include:

- **Ophthalmologists or Retina Specialists**: Experts familiar with ROP and its diagnosis.
- **AI/Data Science Experts**: Specialists in AI and machine learning who can evaluate the performance and accuracy of the deep learning algorithm.
- **Neonatologists or Pediatricians**: To oversee the medical and ethical safety of premature infants in the study.

- **Biostatisticians**: To ensure proper data analysis and interpretation.
- **Ethicists**: To provide guidance on the ethical considerations and participant protection.

Meeting Frequency:

The DSMB should meet biannually and as needed for any safety or ethical concerns.

This board plays a critical role in ensuring the success and ethical conduct of the study while safeguarding the health and safety of the vulnerable population involved

Data Management

Data Collection:

Case Reporting Form (CRF): Medical information of infants will be recorded in electronic Case Report Forms (eCRFs).

Imaging Data: Retinal images obtained using wide-field digital imaging systems will be stored in……..and labeled accordingly for analysis.

Data Management:

All collected data will be securely stored in the cloud or a designated database for easy access and backup. Data entry into CRFs will be completed electronically by SA and will be checked by Co-PIs so as to ensure accuracy and minimize errors. The data will be regularly updated with follow-up information, including any changes in the infant's condition or ROP severity.

References:

1.https://www.who.int/blindness/Vision2020_report.pdf
2. C. Gilbert and A. Foster; Childhood blindness in the context of Vision 2020- the right to sight. Bull World Health Organ.2001; 79(3): 227-232.

3. Hong EH, Shin YU, Cho H. A review of epidemiology and current treatment. Clin Exp Pediatr [Internet] 2022;65(3):115-26. Available from: http://e-cep.org/journal/view.php?doi=10.3345/cep.2021.00773

4. Adhikari S, Badhu BP, Bhatta NK, Rajbhandari RS, Kalakheti BK. Retinopathy of prematurity in a tertiary care hospital in eastern Nepal. JNMA J Nepal Med Assoc. 2008 Jan-Mar;47(169):24-7. PMID: 18552888. https://doi.org/10.31729/jnma.213

5. Shrestha JB et al. Journal of Pediatric Ophthalmology & Strabismus. Vol. 47, No.5, 2010

6. Yadav R, Gupta S, Shrestha JB, Yadav R, Yadav TBS. Perinatal Risk Factors for Retinopathy of Prematurity in Preterm and Low Birth Weight Neonates. Nepal J Ophthalmol. 2020 Jan;12(23):32-38. doi: 10.3126/nepjoph.v12i1.28625. PMID: 32799237. https://doi.org/10.3126/nepjoph.v12i1.28625

PMid:32799237

Appendices: I: NHRC Approval Letter

Government of Nepal

Nepal Health Research Council (NHRC)

Estd. 1991

Ref. No.: 1090

19 November 2024

Dr. Sailesh Kumar Mishra

Principal Investigator, Nepal Netra Jyoti Sangh

Dr. Aeesha Malik

Principal Investigator, London School of Hygiene and Tropical Medicine/International Center for Eye Health (ICEH)

Ref: Approval of research protocol

Dear Dr. Mishra and Dr. Malik,

This is to certify that the following protocol and related documents have been reviewed and granted approval through the expedited review process for its implementation.

Protocol Registration No/ Submitted Date	548_2024 7 OCT 2024	**Sponsor Protocol No**	NA
Principal Investigator/s	Dr. Sailesh Kumar Mishra Dr. Aeesha Malik	**Sponsor Institution**	Velux stiftung /International Center for Eye Health (ICEH)
Title	Evaluating a deep learning algorithm in the diagnosis of retinopathy of prematurity in Nepal and a prediction model for development of ROP		
Protocol Version No	NA	**Version Date**	NA
Other Documents	1. Data collection tools 2. Informed Consent Form 3. Sponsor agreement letter 4. Conflict of Interest (CoI) 5. Permission letter from the site 6. Assent form 7. Ethics Training Certificate 8. Role and responsibilities 9. Work plan	**Risk Category**	Minimal risk
Co-Investigator/s	1. Ranjan Shah 2. Pratap Karki 3. Srijana Basnet Thapa 4. Sabina Shrestha 5. Eli Pradhan		
Study Site	1. Tribhuvan University Teaching Hospital (TUTH), Institute of Medicine, Kathmandu, Nepal 2. Kathmandu Medical College 3. Tilganga Institute of Ophthalmology (TIO)		

Tel: +977 1 5354220,5327460, Ramshah Path, PO Box: 7626, Kathmandu, Nepal
Website: http://www.nhrc.org.np, E-mail: nhrc@nhrc.org.np

Government of Nepal

Nepal Health Research Council (NHRC)

Estd. 1991

Ref. No.: 1090

Type of Review	√	**Expedited**	**Timeline of Study** 19 November 2024 to NOV 2028 **Duration of Approval** 19 NOV 2024 to 18 NOV 2025 **This approval will be valid for one year**	**Frequency of continuing review** Every one year
		Full Board		
	Review Date: 19 November 2024			
Total budget of research	**NRs 16,17,000.00**			
Ethical review processing fee	**NRs 48,510.00**			

Investigator Responsibilities

- Permissions from the study sites is required before initiating the study.
- If you do not start the project within 3 months of this letter, please contact the Ethical Review M & E Section at NHRC.
- Any amendments shall be approved from the ERB before implementing them
- Submit progress report every 6 months
- Submit final report after completion of protocol procedures at the study site
- Comply with all relevant international and NHRC guidelines
- Abide by the principles of Good Clinical Practice and ethical conduct of the research

If you have any questions, please contact the Ethical Review M & E Section at NHRC.

Thanking you,

Dr. Pramod Joshi

Member Secretary

Cc

1. IRC of Tribhuvan University Teaching Hospital (TUTH), Institute of Medicine, Kathmandu, Nepal
2. IRC of Kathmandu Medical College, Kathmandu
3. IRC of Tilganga Institute of Ophthalmology (TIO), Kathmandu

Appendices: II: PIS Form

Nepal Netra Jyoti Sangh

Tripureshwor, Kathmandu

" Evaluating a deep learning algorithm in the diagnosis of retinopathy of prematurity in Nepal and a prediction model for development of ROP"

Patient Information Sheet

[In case the parent(s)/legal representative(s) cannot read, a witness should be present to ensure that the parent information is explained correctly. Read out loud:]

We are asking you to take part with your baby in this study because your baby is at risk of retinopathy of prematurity (ROP). As part of routine medical care, your baby should be screened and regularly monitored for the development of ROP in a timely manner.

Before you decide whether you want to take part in this study, you will be given an explanation about what the study involves. Participation is voluntary. In order to participate your written consent is required. It is important that you read and understand the study procedures, benefits, risks, your right to withdraw and participant's confidentiality. Please take your time to read this information and ask the investigator or attending physician if you have any questions. You can also discuss it with your partner, friends or family.

1.Background of the study

Retinopathy of Prematurity (ROP) is an eye condition that can affect premature babies, where abnormal blood vessels grow in the retina, the part of the eye responsible for seeing. It is estimated that nearly one in four premature babies develop this eye condition. In some cases, it can lead to vision problems or blindness if not treated. However, with early detection and treatment, the risk of severe vision loss can be reduced. Babies are usually screened starting around 4-6 weeks after birth, or at 31-33 weeks of gestational age, and follow-up exams continue every 1-2 weeks until the retina is fully developed, or treatment is no longer needed. For babies with more severe cases, the follow-up may be more frequent and continue for a longer period

2.Aim of the study

The study aims to assess the effectiveness of an artificial intelligence (AI) system on detection of ROP. Additionally, there is a plan to evaluate the performance of a new, simple and cost-effective smartphone-based diagnostic tool for ROP in a later phase.

3. General information

This study is carried out by Nepal Netra Jyoti Sangh (NNJS) in collaboration with Tilganga Institute of Ophthalmology (TIO), Kathmandu Medical College (KMC), Tribhuvan University Teaching Hospital (TUTH) and other partner hospitals. Three hospitals from Kathmandu valley namely TIO, KMC and TUTH are participating in this study. Nearly 700 premature infants will be participating in this study. All eligible patients, whether admitted to the participating hospitals or visiting the outpatient departments (OPD) will be invited to participate. Ethical approval has been granted by the Ethics Review Board (ERB) of NHRC, along with additional approvals from the hospitals involved. The study is being carried out by trained ophthalmologists, ophthalmic assistants, and data enumerators to ensure accuracy and reliability of the results.

4.What does participation in this study involve?

Participation in this study is entirely voluntary. The process of obtaining retinal images of your baby and interacting with you will take no more than 20 minutes. Additionally, you are requested to provide deliberate and honest answers to all questions posed during the study. Your participation and accurate responses are crucial for the success of this research.

Please note that the retinal images of your baby will be shared with the international study team for research purposes. Furthermore, the medical information of your baby will be recorded, and we kindly request you to provide your consent for this process to ensure a comprehensive understanding of your baby's condition.

As the risk of ROP continues for several weeks after birth, you need to bring your baby for the follow up retinal examination and we will collect retinal image of your baby during follow up visit as well. You will get reminder phone call from the research team to come for OPD visits.

5 What are the risks and benefits of the study?

Your cooperation and support in this study are essential for enhancing ROP services across eye hospitals in Nepal and beyond. Your participation will contribute to enhancing ROP care by aiding in the development of a simple diagnostic tool, develop timely strategies for eye care, and expand services to address this critical issue. We would like to assure you that there are no risks associated with participating in this study, nor will you receive any direct benefits such as cash or gifts. However, if your baby develop ROP and need any medical treatment, such as AntiVEGF injections or laser therapy, the treatment expenses will be covered from the study.

6.How will my information be kept private?

Data collected through your child's retinal images and your responses will be kept confidential and used solely for a study of national importance. Your name, your child's name, address, and personal or clinical details will not be published in any reports or communications; only an introductory code will be used. Your support and cooperation are crucial for the formulation and development of eye-related policies. Therefore, you are requested to answer all questions deliberately and truthfully.

7. Can I leave the study if I change my mind?

You can change your mind any time you want, also after your decision to participate. If you want your information removed from the study, you can contact us. You do not have to provide a reason for stopping. The data that have been collected until the time you withdraw your consent will still be used in the study. Your decision to be in this study or not will not affect the health care your baby. If there is any new information about the study that is important for you, the research team will inform you of this. You will then be asked if you wish to continue your baby's participation.

8. End of the study

Your baby's participation in the study ends when his/her retinal matures which typically ranges from several weeks to a few months, depending on the severity of the condition. The entire study ends when the last participant has finished with the study.

9.Who can I call if I have questions about the study?

If you have any questions or concerns regarding the study, please feel free to contact the study team at any time. For more details, you can reach the Central Office of Nepal Netra Jyoti Sangh in Tripureshowr, Kathmandu at Tel: 01-5361066.

If you would like independent advice about participation in this study, please get in touch with the independent doctor. He knows a lot about the study but has nothing to do with this study.

If you have any complaints about the study, you can discuss this with the investigator or your regular doctor. Or you can directly reach out to the ERB of NHRC at 01-5354220; Email: approval@nhrc.gov.np for the any inquiries or appeals related to ethical violations or human rights you can contact.

10.Signing of informed consent form

When you have had a sufficient reflection period, you will be asked to decide about participation in this study. If you consent, you will be asked to confirm this on the corresponding consent form, in writing. With your written consent, you indicate that you have understood the information and agree to participate in the study.

Thank you for your attention.

Yours sincerely,

Dr. Eli Pradhan

Dr. Srijana Basnet

Dr Pratap Karki

Study Team

Consent Form for parents or legal representative

Participant ID

I understand the objectives and background of this study, including the interview process, my roles and responsibilities, potential risks and benefits, and confidentiality measures. I am aware that retinal images of my baby will be taken and will be shared with an international research team, and I will also participate in an interview because my baby was born prematurely and may be at risk for Retinopathy of Prematurity (ROP). I acknowledge that my and my baby's personal and medical/clinical details will also be collected keeping confidential and used solely for research of national importance. I have been informed that I can choose to skip any question or withdraw from the study at any time. I have received this information through either reading the consent form myself (…….) or having it read to me by the interviewer (…….).

Name of parent/ legal representative:……	Name of investigator or his/her representative……..
Signature:……	Signature:……
Date: ___(day)/ ___(month) / _____(year)	Date: ___(day)/ ___(month) / _____(year)

In case parent(s)/legal representative(s) cannot read, a witness should be present to ensure that the parent information is

explained correctly:

Name of witness……..

Signature:……

Date: ___(day)/ ___(month) / _____(year)

I hereby certify that I have informed the above person/persons fully about the said study. If information becomes known during the study that could influence the consent of the parent or legal representative, I will inform him/her of this on time.

Name of investigator or his/her representative……..

Signature:……

Date: ___(day)/ ___(month) / _____(year)

Appendices: II: Proforma

ARTIFICIAL INTELLIGENCE FOR THE DIAGNOSIS OF RETINOPATHY OF PREMATURITY (ROP)

CASE REPORTING FORM

Date of Screening: OPD no: Study ID no: Contact no:

Study site: ☐ TUTH ☐ KMC ☐ BPKLOCS ☐ TIO

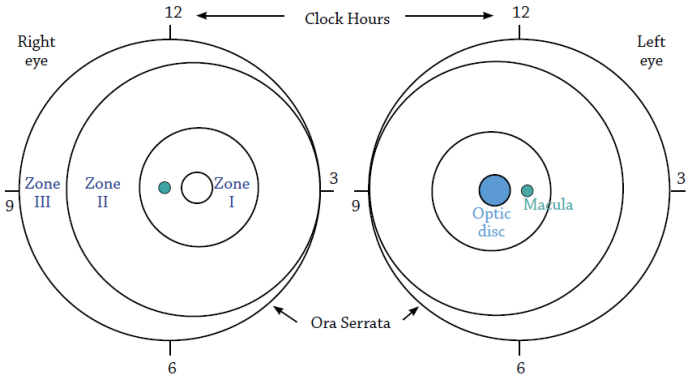
Identification					
Baby of:	Date of birth:	Birth weight (gms):	Gestational age at the time of birth:	Weeks and days:	Sex: M/F

Risk Factor

Perinatal History: Mode of Delivery: ☐ Vaginal ☐ Cesarean Mode of conception☐ spontaneous ☐ Assisted Specify if assisted_____ Multiple births: ☐ Yes ☐ No, Order:_____ Apgar Scores: _____(1 min) / _____ (5 min) Antenatal Steroids: ☐ complete ☐incomplete ☐none Maternal Diabetes: ☐ Yes ☐ No Maternal Hypertension: ☐ Yes ☐ No Maternal Smoking: ☐ Yes ☐ No Maternal Infection (e.g., Chorioamnionitis): ☐ Yes ☐ No Premature rupture of membrane ☐ Yes ☐ No	Neonatal Factors: Oxygen Therapy: ☐ Yes ☐ No If yes, duration: _____ days Oxygen Saturation Target: _____ % Mechanical Ventilation: ☐ Yes ☐ No If yes, duration: _____ days Continuous Positive Airway Pressure (CPAP): ☐ Yes ☐ No If yes, duration: _____ days Blood Transfusions: ☐ Yes ☐ No If Yes specify blood product and number of unit:_____ Sepsis: ☐ Yes ☐ No ☐Clinical ☐Screening proven ☐ Culture proven Necrotizing Enterocolitis (NEC): ☐ Yes ☐ No Intraventricular Hemorrhage (IVH): ☐ Yes ☐ No Patent Ductus Arteriosus (PDA): ☐ Yes ☐ No If yes, treatment: ☐ Medical ☐ Surgical Cardiovascular defect other than PDA(specify)_____ Apnea: ☐ Yes ☐ No no. of episodes:_____ Hyperglycemia: ☐ Yes ☐ No Hypotension: ☐ Yes ☐ No If yes, treatment: ☐ Yes ☐ No Kangaroo Mother Care

	☐ none ☐ Short (<4hrs/d) ☐ long (≥4hrs/d)

Date of Screening:	Current Gestational Age:	Current weight:	Study ID no:	1st examination



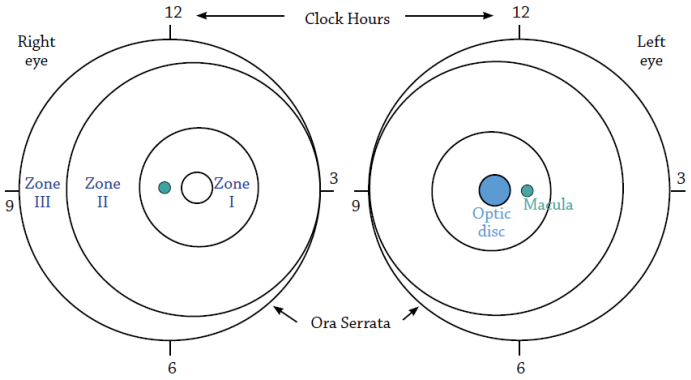
Right Eye							Left Eye						
Mature Retina	Immature, No ROP	Zone	Stage	Plus	AP	Type	Mature Retina	Immature, No ROP	Zone	Stage	Plus	AP	Type
Remarks													
Recommendation	Type of treatment: ☐ Laser Therapy ☐ Anti-VEGF Therapy ☐ Surgery Additional Notes: _____ _____ Next follow-up date:_____												

ARTIFICIAL INTELLIGENCE FOR THE DIAGNOSIS OF RETINOPATHY OF PREMATURITY (ROP)

FOLLOW UP CASE REPORTING FORM

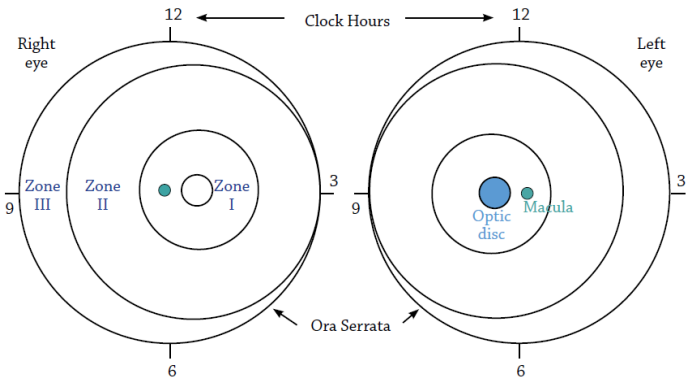
Study site: ☐ TUTH ☐ KMC ☐ BPKLOCS ☐ TIO

Date of Screening:	Current Gestational Age:	Current weight:	Study ID no:	Follow-up no:



Right Eye							Left Eye						
Mature Retina	Immature, No ROP	Zone	Stage	Plus	AP	Type	Mature Retina	Immature, No ROP	Zone	Stage	Plus	AP	Type
Remarks													
Recommendation	Type of treatment: ☐ Laser Therapy ☐ Anti-VEGF Therapy ☐ Surgery Additional Notes: _____ _____ Next follow-up date:_____												

Date of Screening:	Current Gestational Age:	Current weight:	Study ID no:	Follow-up no:



Right Eye							Left Eye						
Mature Retina	Immature, No ROP	Zone	Stage	Plus	AP	Type	Mature Retina	Immature, No ROP	Zone	Stage	Plus	AP	Type
Remarks													
Recommendation	Type of treatment: ☐ Laser Therapy ☐ Anti-VEGF Therapy ☐ Surgery Additional Notes: _____ _____ Next follow-up date:_____												