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RESEARCH COLLABORATION AGREEMENT

This Research Collaboration Agreement ("**the Agreement**"), having an "Effective Date" of _____, is made between Indian Council of Medical Research located at V Ramalingaswami Bhawan, Ansari Nagar, New Delhi, India ("**ICMR**") through its Division of Epidemiology and Communicable Diseases ("**ECD**") and Institute for Plasma Research located at Bhat Village, Near Indira Bridge, Gandhinagar, Gujarat, India ("**IPR**") under the following terms and conditions.

Collectively ICMR and IPR shall be referred to as "**Parties**".

1. **Research Project**. India TB Research Consortium ("**ITRC**"), is an initiative being led by ICMR, which aims to bring together diverse stakeholders to develop new tools – diagnostics, vaccines and drugs – to enable India to take a leadership role in fast-tracking translational TB research and realizing TB eradication (Hereinafter referred to as "**Research Project**"). Tuberculosis prevalence Survey is being undertaken in a big way by ICMR along with ICMR's Institute – National Institute for Research in Tuberculosis, Chennai ("**NIRT**") in collaboration with MOHFW and WHO to find out the TB prevalence in the country. The survey would cover a population of 5,00,000 from 625 clusters from across the country over a period of one year. IPR on the other hand is involved in development of Artificial Intelligence/ML/DL based applications and is currently developing an Artificial Intelligence Tool, which will be helpful for Medical imaging. The ECD Division of ICMR and IPR desire to undertake collaborative activities for effective implementation of the Research Project and associated collaboration for Tool development. The Nodal Officer for the Research Project for ICMR will be Dr. Manjula Singh, Scientist- E, ECD, ICMR Headquarters along with Dr. Srikanth Tripathy, Director NIRT, Chennai. The Nodal Officer for IPR will be Ms. Manika Sharma, Scientific Officer- G, Head Multi-Disciplinary Research Division, Institute for Plasma Research, Gandhinagar, Gujarat. Taking note of the respective activities, IPR and ICMR jointly desire to deploy the tool enabled by Artificial Intelligence that IPR is developing ("**AI Tool/ Tool**") for fast automated screening/detection of Tuberculosis for the AI Tool in National TB prevalence survey. ICMR along with NIRT, Chennai is to provide data and IPR will use the data for the AI Tool.

2. **Confidentiality**. Subject to paragraph 4, below, during the term of this Agreement and for a period of five years thereafter, each party shall cause all information that is disclosed to it by the other party in connection with the Research Project and is identified in writing as confidential by the disclosing party ("**Confidential Information**") to be treated according to the same internal security procedures and with the same degree of care regarding its secrecy and confidentiality as the party receiving the disclosure treats similar information of its own within its organization. Confidential Information does not include information that: (i) is or later becomes available to the public through no breach of this Agreement; (ii) is obtained from a third party who had the legal right to disclose the information; (iii) as of the date of disclosure, is already in the possession of the party to whom disclosure is made; or (iv) is required to be disclosed by law, government regulation, or court order.

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3. **Responsibilities of the Parties.** Each party is an independent contractor and has no authority to bind or act on behalf of another party. Both Parties will be responsible for the committed resources and meeting the expenses towards their respective activities. Both the Parties agree for third Party Validation (External Validation) during the conduct of the Prospective study.

3.1 **Responsibilities of ICMR.** ICMR along with NIRT shall be responsible for providing the data for the assessment/validation and further development of the AI tool and conduct of the Prospective validation studies. ICMR shall provide funding to sites involved thereto in the Research Project. If necessary, ICMR shall grant remote access to IPR scientific Officers for effective trouble shooting of technical issues while implementing the scope of the present Agreement. Third Party validation of the AI Tool shall be undertaken by ICMR who shall also fund the operational aspect of the same. All statutory/ethical/other clearances will be done by ICMR

3.2 **Responsibilities of IPR.** IPR shall fund the requisites and operational aspects including those related to spending towards the Trainers to be engaged for training of the technical operators /staff of the Survey vans/buses and the central data center for the AI tool installation and usage for its assessment/validation. The categories to be included in the assessment matrix is provided for under the **Annexure A.** Initial deployment for the enabling ecosystem by the IPR shall be in such number of the survey vans/ buses/ sites and at such places where the training of the technical operators and other staff becomes feasible. Trained operators and staff can then be deployed in different vans/ sites including those at the remote areas. Training by IPR can be in one or two sittings depending on the extent of tool usage requirement. IPR does not have any objection to the third party validation of the AI Tool by ICMR and it shall support the Tool's technical facilitation aspects. IPR will complete the preliminary development of the AI Tool for using the ICMR Data and internal validation. IPR will provide the final version of the AI Tool for third Party validation. IPR shall provide the Tool free of cost for the Research Project only and subsequently for the National Programme for TB elimination, if successful and not for any other purpose. The developed AI software will only be a 'tool' to provide advice to Radiologist and Doctors and the Radiologists and Doctors are expected to use their own discretion whether to apply the tool for medical practices on patients. IPR has not made any representation as to the accuracy and efficiency of the tool. In light of this, IPR will in no manner whatsoever be held responsible for any adversarial action taken by any party from the output of the software.

In the event there is any ambiguity with regard to the scope of the responsibilities, the respective Nodal Officers are expected to clarify the same and sort out the issue so that the main aim of this Research Project is not lost and the Research Project is not abandoned.

4. **Outcome of Research Project.**

In General. Each party will keep the other party informed of research outcome obtained from implementation of the Research Project. Information shared in accordance with this

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paragraph shall be treated as confidential by the party to which it is disclosed (even if not identified as confidential by the disclosing party), and shall be handled by that party in accordance with, the terms of paragraph 2, above.

Inventions. For purposes of this Agreement, an "Invention" is any algorithm/ workflow/ pipeline/ software module through deep learning related to scope of the project, whether patentable or nonpatentable, or copyrightable or non-copyrightable, that is conceived or reduced to practice. The pre-existing Invention that has been conceived or reduced to practice independently by any of the Party before initiation of the activities under this Agreement shall be the "Back ground Invention" and shall belong to the respective Party. Any Inventorship of Invention conceived or reduced to practice in the course of the Research Project shall be treated as "Joint Invention" of both the parties. The results/outcome of the project, after securing Intellectual Property Rights, shall be made available to public, as per Global access principles.

Global Access requires that

a) The knowledge and information gained from the Research Project be promptly and broadly disseminated

b) If successful, the Research Developments including the Joint Invention is made available and accessible at free of cost for the TB National Program and at affordable price to people most in need within developing countries.

c) In this regard, it will be ensured that the above Global Access provisions shall be incorporated in all relevant present and future research and development agreements in a suitable form.

Publication. It is contemplated that outcome/algorithm/workflow/ pipeline/software module etc. related to scope of the project will be jointly published. The parties agree to abide by the policies of journals in which publications will appear. Authorship of results of the Research Project will be determined in accordance with academic standards and mutual agreement. Proper acknowledgment will be made for the contributions of each party to the research being published within the scope of this agreement. In addition, a party will not publish Confidential Information received from the other party without other party's consent.

5. ***Force Majeure***

The Parties shall not be held responsible for non-fulfillment of their respective obligations in successful completion of the Project under this Contract due to the exigency of one or more force majeure events such as but not limited to acts of God, war, flood, earthquakes etc.

6. **Indemnification**

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The Parties have no obligation to indemnify the other for claims, actions, demands, suits, losses, liabilities, judgments, expenses or costs (including attorneys' fees) made by third parties arising out of or related to this Agreement.

7. **Compliance with Laws and Regulations**. All research done in connection with the Research Project, including all use of Research tools, materials or Data transferred hereunder will be done in compliance with relevant regulations, guidelines and laws of the Government of India as may be in force from time to time.

8. Non-exclusivity. The present arrangement for research with the AI Tool is not exclusive and the Parties can have similar arrangements with any third party in unrestricted manner.

9. **Term of Agreement; Duration of Research Project**. This Agreement shall come into effect on the Effective Date and shall continue to be in effect for five years thereafter or until the Research Projects are completed or terminated whichever is earlier. ICMR or IPR may terminate this Agreement at any time upon 30 days' written notice to the other party, regardless of whether the Research Project has been completed. In the event of Termination, the Parties agree to negotiate termination conditions to enable clear severance of subsisting obligations related to public health and return of confidential Data as on date.

Various proposals under this MoU may be taken up in a time bound manner in view of combating TB by 2025. In initial part, the following two milestones are proposed in phase1.

9.1 Phase 1 :

Milestone 1: Initially it is proposed that it will consist of use of retrospective validated data provided by ICMR/NIRT for development of the tool to differentiate between normal from abnormal chest x ray and then segregate the X-rays with suspected TB lesions. (timelines: 2 – 4 months) . After the completion of Milestone 1 and it's validation by ICMR/NIRT milestone 2 will be taken up.

Milestone 2: In this Milestone an algorithm would be built that would detect tuberculosis with great accuracy including differentiation of all possible clinical variants of tuberculosis and also differentiate from other non-tuberculous diseases like silicosis, pneumonia. (Timeline: 9-12 months)

9.2 Phase 2:

- Prospective validation of AI tool developed in Milestone 1 in survey vans (6-8 months)
- Prospective validation of AI tool developed in Milestone 2 at hospital and community based settings (9-12 months)

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10. **Use of Name.** The Parties shall not use the name or names of institutions or investigators, or any abbreviation or variant thereof, in any press release, or in any commercial advertisement or similar material that is used to promote or sell products or services, unless obtain in advance the written consent of the named party to such use.

11. **Assignment.** This Agreement is not assignable by a party, whether by operation of law or otherwise, either in whole or in part, without the prior written consent of the other party.

12. **Disputes. The governance of the Agreement shall be amenable to the Jurisdiction of Delhi.** Disputes arising in the implementation of this agreement and during the course or after the research project shall be resolved through mutual consultations and negotiation. However, if mutual consensus is not reached, the disputes would be resolved as per the joint decision of Director General, ICMR and Director, IPR. Such joint decision shall be final and binding on both the Parties.

Agreed by:

DIVISION OF ECD

INDIAN COUNCIL OF MEDICAL RESEARCH

By: _____

Name: Dr Abdul Mabood Khan

Title: Scientist G & Head ECD-II

13/04/2020

National Institute for Research in Tuberculosis

By: _____

Name: ERIKAVUM TRIPATHY

Title: Director-in-Charge, ICMR-NIRT

Date: 8/4/20

Institute for Plasma Research

By: _____

Name: SHASHANK CHATURVEDI

Title: DIRECTOR

Date: 8/4/20

Read and acknowledged:

_____

[Witness 1]

Date: _____

_____

[Witness 2]

Date: _____

Annexure A

Scope of work

Project entitled "Development Of Artificial Intelligence Tool For Screening/detection of Pulmonary TB using Chest X-rays".

1) Title of the project

Development of an artificial intelligence tool for automated detection/screening of pulmonary tuberculosis using chest x ray.

2) Aims and Objectives

AIM: To develop a computer-aided detection (CAD) system for screening and diagnosis of TB using chest x-rays for use in peripheral settings under national Programme.

Objectives:

- To develop an computer assisted screening system to differentiate clinically normal chest x ray from clinically abnormal types.
- To develop a computer aided detection system that enables auto differentiation of TB chest x ray from other X-rays from patients of other lung diseases
- To further develop the computer aided detection system for auto identification of different variants of pulmonary tuberculosis.

3) Rational of project

India is the leading contributor of global tuberculosis burden as per WHO report 2019. Efficient and timely screening of tuberculosis at peripheral health sector level and remote India is still an incessant challenge the health sector is facing. This gap is greatly contributed by unbalanced doctors/trained physicians and patient ratio[5] as well as non-availability of cost effective, user friendly and robust diagnostic tools that can identify tuberculosis in a fraction of a minute. Hence, development of an AI Tool is the need of hour to bridge this diagnostic gap and facilitate affected individuals reach the management centers at earnest therefore contributing to the national interest of combating tuberculosis by 2025.

AI is the area of computer science that helps in development of tools that can mimic human like thought processing, reasoning and self -correction abilities [6]. Artificial intelligence technologies include training of tool and deep learning.

Deep learning is a particular kind of machine learning that achieves great power and flexibility by learning to represent the world as nested hierarchy of concepts, with each concept defined in relation to simpler concepts, and more abstract representations computed in terms of less abstract ones.[4]

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4) **Preliminary work already done by the developers.**

ICMR since its inception have been proactively involved in taking forward any innovative and promising ideas that have potential to cater to larger national interest in health sector. AI for health is an important area of research and that requires large amount of data for development or validation of any AI tool. ICMR being the top most government research body in the country conducts, promotes and co-ordinates research in the country and abroad through intramural research through its 33 permanent Institutes across the country and through extramural research by funding other medical organizations and research Institutes. TB is the most common and largest killer among the infectious diseases in the world. TB detection being a common challenge, it is important to develop tools that can aid detection of TB specially in remote areas. ICMR-NIRT, Chennai has access to large amount of data related to Chest X-rays from the earlier prevalence survey conducted in South India besides the data emerging from various studies and clinical trials. Also ICMR is parallelly conducting a Nationwide TB prevalence survey this year that intends to screen five lakh general population using chest x ray from 625 clusters across India. **Therefore it is planned to utilize this data set with others for development, learning and further training of the AI Tool.**

Artificial Intelligence Software has been developed by IPR and currently is able to detect abnormal Chest X-rays from the normal X-rays. However the data set used for the same has been insufficient and the software needs to be trained on large amount of data sets. The tool further need to be developed for fast Automated Screening of TB (X-Ray, Sputum) to automatically detect foot print of Pulmonary Tuberculosis in Chest X ray. The tool developed by IPR can analyze 10 X ray images in 1 min using single laptop. The software unlike most of its counterparts is cloud independent, that underscores its advantage that it can be used in area with poor internet services using common desktops /laptops. The tool however needs extensive learning on a significantly large data set.

Understanding the importance of the tool, it was suggested to take forward the AI Tool that is being developed by Institute for Plasma Research Ahmedabad, an allied research agency under department of Atomic Energy, Government Of India for further development to differentiate between TB and other abnormal X-rays.

5) **Links with other projects**

ICMR and NIRT have been conducting several studies that would have large amount of data including the Chest X-rays from the TB cases and other contacts. The normal x- ray and abnormal x- ray taken from TB patients at the Tiruvallur TB Surveillance during 2016 -2018 would also be utilized for the learning by the software. Possibility of collecting x ray from other private hospitals and district hospitals under Central TB Division, GOI, will also be explored.

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6) **Detail research plan**

The AI tool currently with IPR is able to differentiate a normal Chest X-ray from an abnormal X-ray. This will be further developed jointly by Indian council of Medical Research and NIRT Chennai and institute for plasma research after signing an MOU, to differentiate and detect TB from a set of abnormal Chest X-rays. The work related to further training and development of the AI tool will be primarily done at Institute for Plasma Research and the data sets would be provided by ICMR, NIRT and other Institutes, if required. **ICMR, headquarters will remain the central coordinating institute, ICMR and NIRT Chennai would provide the data.** The x- ray data set already available with NIRT, Chennai would be used for the development of the tool. Further data generated during National TB prevalence survey will be used for this project for training and validation. In this prospective survey, 5,00,000 population would be screened for TB and the radiological presentation of the suspected cases of TB would be confirmed by clinical examination and laboratory tests like sputum AFB and liquid culture testing. In addition, the x- ray films will be read and the diagnosis confirmed by two tele-radiologists.

The Research Plan shall be read in line with the responsibilities of the collaborators as provided for in the associated Research Collaboration Agreement.

A) AI Tool Development Plan:

Role of IPR

Phase 1: (Development of tool: (learning and training)

This would consist of the following Milestones:

Milestone 1: Initial proposal would consists of the use of retrospective validated data provided by ICMR/NIRT for development of the tool to differentiate between normal from abnormal chest x ray and then segregate the X-rays with suspected TB lesions. (timelines: 2 – 4 months) . After the completion of Milestone 1 and it's validation by ICMR/NIRT, milestone 2 will be taken up.

Milestone 2: This milestone would be undertaken wherein an algorithm would be built that would detect tuberculosis with greater accuracy including differentiation of all possible clinical variants of tuberculosis and also differentiate from other non-tuberculosis diseases like silicosis, pneumonia. (Timeline: 9-12 months)

Phase 2: (Validation/testing of tool)

This phase consists of the following components and included prospective validation and user feedback in terms of accuracy of interpretation and feasibility. Validation of the developed tools as mentioned above in field conditions would consist of two components:

a) The AI tool developed in Milestone 1 to differentiate between normal from abnormal chest x ray would be taken up for validation in ongoing survey vans that should take 6-8 months to as long as the survey continues till its completion.
b) The AI tool developed in Milestone 2 to differentiate tuberculosis including differentiation of all possible clinical variants of tuberculosis and also differentiate from other non-tuberculous diseases like silicosis,

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pneumonia. This prospective validation in hospital and community based settings should be performed in 6-9 months time.

Phase 3-Deployment under National Program.

This would consist of the final deployment of the tool under National Programme for detection of the TB in primary health cate centers/remote centers. This would include the following:

- Deployment of the tool at primary health care level after development in phased manner and establish process for its continuous maintenance.
- Response to all the queries related to the tool

TECHINICAL DESCRIPTION OF TOOL DEVELOPMENT PROCESSES

Deep CXR is an Artificial Intelligence software for automated screening of footprints of tuberculosis in Chest X-Ray images. The AI based software developed by IPR comprises of pre-trained model with customized learning parameters for training the chest X-Ray image dataset. The software in the first stage converts all the input image files to jpg/png file format irrespective of initial extension. Then an image enhancement tool based on histogram equalization is applied to normalize and improve the quality of all the input images. An in-house code is written by IPR to crop the chest region from the enhanced image. A first layer of the deep learning model is applied to extract the left/right region of the cropped chest X-Ray images. Finally, a second layer of the deep learning model is applied to classify the extracted regions in normal/abnormal category which is saved in external/internal disk drive.

B) Role of ICMR: Providing Data

ICMR would provide the data set to IPR for training of the artificial intelligence tool. The data set here would include the retrospective data which includes validated Chest X-rays collected from earlier surveys. The prospective data set would include the data collected prospectively from the ongoing national TB Prevalence survey and may have information related to demographics, variation as per geography, variability as per occupation, gender, age and other diseases and type of TB.

All data will be collected and managed at ICMR/NIRT before being sent to IPR. The collected data will be anonymized. This is in accordance with privacy and data security policy of ICMR.

Data for Phase 1 Milestone 1 :

- In first phase and in milestone 1 a data set (comprising of about 20000 or more validated and annotated normal and abnormal chest x rays) will be provided to IPR for initial training of the tool.
- Confirmed non-TB/normal and cases would also be provided for improving the specificity.
- Additional data may be required depending on preliminary result obtained from the given data set.
- The IPR and ICMR would discuss and do a detailed analysis of the different variants and conditions which would be seen in X-Rays and would prepare the details on the number and type of x-rays required for the training.

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Data for phase 1 Milestone 2 :

Development Plan: Collection of data sets for training:

Type of X-rays and clinical co-relation with TB including the Category Matrix:

1. Chest x ray will be read and assigned to one of the following categories by the identified clinicians at ICMR institute. The X-rays would be annotated with clear demarcation of the lesion with identification. Additional data may be required depending on preliminary result obtained from first data set. The data set would consist of the following:
2. Normal chest x ray with no notable finding. **(approx.. 4000-5000 for initial learning and training)**
3. Chest X-rays from clinical variants of pulmonary tuberculosis cases with laboratory confirmed sputum positive and radiologically confirmed -belonging to following types/ categories. The number of X-rays for clinical variants will be obtained (approximate number as mentioned below or more, if available for initial learning and training. For some of the rare variants, the number might be less).

a) Primary tuberculosis pneumonia/ Consolidation	(1000)
b) Tuberculosis pleurisy/ pleural effusion	(500)
c) Cavitary tuberculosis	(1000)
d) Miliary Tuberculoisis	(200)
e) Tubercular fibrosis	(500)
f) Tubercular scar/fibrocalcific scar	(200)
g) Apical TB	(200)
h) Calcification or infiltration	(200)
i) Nodule with poorly defined margin	(500)
j) Hilar or mediastinal lymphadenopathy	(200)
k) Linear, interstitial disease (in children only) or Discrete linear or reticular densities within the lung for old TB	(100)
l) Post-TB atelectasis	(200)
m) Others like bronchiectasis	(500)
n) Drug resistant TB	(500)

4. Sputum negative but radiologically confirmed pulmonary tuberculosis (approx. **1000 for initial learning)**

5. Non-tuberculous chest x ray that may resemble TB (approx. **1000 for learning** and training) may include the Non-TB lesions in X-rays (like Nodular, Consolidation, pleural effusion, cavitation, Miliary lesions like occupational silicosis, fibrosis, scar, calcification and silicosis)

Additional information: Demographic and other details for the collected data to build clinical support system

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a) Age
b) Sex
c) B

IPR would provide support for the following

- Train technicians at NIRT Chennai to anonymize the data and anonymize the data set provided at NIRT Chennai
- Discuss the variants of Chest TB and recalculate the statistical number of chest x rays needed for individual variants of tuberculosis to train the tool.

Test data sets:

The test data set would be prepared and kept ready for the testing of the tool. After learning and validation, tool would be tested on undisclosed data sets and based on results would be placed in National TB Prevalence Survey buses for initial screening of the Chest X-rays in the field. Depending on the sensitivity of the test data, the tool could also be taken up for further validation in a prospective study which would be population and hospital based study.

7) Assessment of the performance of tool

The assessment of the performance would be done on test data set in terms of sensitivity and specificity of the artificial intelligence tool .

8) IMPACT ASSESSMENT

- Progress: Evaluation of the progress (programmatic and technical progress) in the integration and use of AI Tool for automated detection of TB in India
- Outcome: Presentation of the outcome of the AI Tool for automated detection of TB project to the collaborating partners in futures.

9) EXPECTED OUTCOME

The final version of the tool will greatly facilitate bridging the gap between diagnosis and treatment more so in economically or geographically difficult population and hence significantly cater to the National Goal of Eliminating Tuberculosis By 2025 as well as END TB Strategy of the Sustainable Development Goals

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Agreed by:

DIVISION OF ECD

INDIAN COUNCIL OF MEDICAL RESEARCH

By: _____

Name: ABDUL MABOOD KHAN

Title: Scientist 'G' & Head ECD-II

Date: 13/04/2020

National Institute for Research in Tuberculosis

By: _____

Name: ERIKANTH TRIPATHY

Title: Director-in-charge, ICMR-NIRT

Date: 8/4/20

Institute for Plasma Research

By: _____

Name: SHASHANK CHATURVEDI

Title: DIRECTOR

Date: 8/4/20