Research Protocol:

Development and Evaluation of an Artificial Intelligence Model for Cervical Cancer Detection from Colposcopic Images

Principal Investigator:

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Co-Principal Investigator:

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Date of Submission

12 / 20 / 2023

Application for Ethical Clearance

Ibn Sina Medical College
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1. Principal Investigator(s):

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3. Place of the Study/Institution(s):

i. Ibn Sina Medical College Hospital, Kallyanpur
1/1, Mirpur Road, Kallyanpur, Dhaka-1216

ii. Ibn Sina Diagnostic & Imaging Center, Dhanmondi
House 48, Road 9/A, Dhanmondi, Dhaka-1209

Other national/international medical institutes if needed.

4. Title of Study: Development and Evaluation of an Artificial Intelligence Model for Cervical Cancer Detection from Colposcopic Images

5. Type of Study: Prospective and retrospective case-control study.

6. Duration of Study: 6 months

7. **Total Cost:** N/A

8. **Funding Agency:** N/A.

I agree to obtain approval of the Ibn Sina Ethical Review Committee for any changes involving the rights and welfare of subjects or any changes of the Methodology before making any such changes.

_____

Dr. Taufiq Hasan
Associate Professor, Biomedical Engineering,
Bangladesh University of Engineering and Technology (BUET), Dhaka – 1205.
Date: 12/20/2023

_____

Prof. Dr. Nasrin Ara Zaman, MBBS, DGO, FCPS (Obs & Gynae)
Obstetrics & Gynecology Specialist & Surgeon
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Date: 12/20/2023

Circle the appropriate answer to each of the following
(If not Applicable write NA)

1. Source of Population:

(a) ILL Participant (Yes) No

(b) Non ILL Participant (Yes) No

(c) Minors or persons under guardianship (Yes) No

2. Does the study involve?

(a) Physical risks To the subjects Yes (No)

(b) Social Risks Yes (No)

(c) Psychological Risks to subjects Yes (No)

(d) Discomfort to Subjects Yes (No)

(e) Invasion of the body Yes (No)

(f) Invasion of Privacy (Yes) No

(g) Disclosure of Information damaging to Subject or others (Yes) No

3. Does the study involve?

(a) Use of records, (Hospital, medical, Death, birth or other) (Yes) No

(b) Use of fetal tissue Or abortus Yes (No)

(c) Use of organs or Body fluids Yes (No)

4. Are subjects clearly informed about?

(a) Nature and purposes of study (Yes) No

(b) Procedures to be followed including alternatives used N/A

(c) Physical risks N/A

(d) Private questions (Yes) No

(e) Invasion of the Body N/A

(f) Benefits to be Derived (Yes) No

(g) Right to refuse to participate or to withdraw from study (Yes) No

(h) Confidential handling of data (Yes) No

(i) Compensation where there are risks or loss of working time or privacy is involved in any particular procedure (Yes) No

5. Will signed consent form/verbal consent be required?

(a) From Subjects (Yes) No

(b) From parent or guardian (if subjects are minors) (Yes) No

6. Will precautions be taken to protect anonymity of subje (Yes) No

RESEARCH PROTOCOL

- **Project Title:** Development and Evaluation of an Artificial Intelligence Model for Cervical Cancer Detection from Colposcopic Images

Summary: Cervical cancer currently poses a significant health threat due to late-stage diagnosis leading to higher mortality rates and limited access to timely screenings, especially in underserved populations. In context, colposcopy is a screening method to visually examine the cervix, vagina and vulva using a colposcope for signs of cancerous or precancerous cervix tissue. Colposcopy, which is used for further examination of women with abnormalities from the cytology or HPV test, is based on the interpretation of cervical images from colposcope [1]. Three kinds of cervical images are used for visual inspection, including the saline image, acetic acid image and iodine image [2]. Although official organizations have released standards and quality control for colposcopy practice [3], [4], [5], the diagnoses are mainly dependent on the experience of doctors, which is subjective and has poor repeatability [6]. Additionally, it was reported that the visual inspection was inaccurate, even by experienced doctors. The gold standard for the diagnosis of cervical lesions is colposcopy-directed biopsy with histopathological confirmation, however, it is invasive and may cause complications such as bleeding or infection. Thus, an objective, and accurate cervical screening approach based on existing clinical examinations is needed.[7]
As traditional vision screening from colposcopy has risks of misdiagnosis and has low accessibility for time and personnel constraints, the primary focus is on leveraging advanced computational techniques to automate the analysis of colposcopy images, addressing the limitations inherent in traditional vision screening approaches.
By utilizing deep learning methods, we aim to create a model that surpasses the accuracy of vision assessments, providing a reliable and efficient means of identifying transformation zones and detecting early signs of cervical abnormalities.

Central to the aim of this research is the recognition of the pressing need for scalable and cost-effective solutions in low-income settings. The proposed deep learning model seeks to mitigate the shortage of trained personnel by automating the intricate process of colposcopic image analysis. This not only streamlines the screening process but also enables its widespread implementation, making cervical cancer screening more accessible to a larger population.
The research further aims to incorporate domain adaptation techniques, to ensure that the developed model is not only accurate but also robust across different health facilities, accounting for the unique challenges posed by resource constraints, equipment variations, and demographic diversity.

- **Introduction:** Colposcopy is a medical diagnostic procedure to visually examine the cervix as well as the vagina and vulva using a colposcope. The main goal of colposcopy is to prevent cervical cancer by detecting and treating precancerous lesions early. Human Papillomavirus (HPV) is a common infection and the underlying cause for most cervical cancers.
  Globally, cervical cancer is the fourth most common cancer in women, with 604,000 new cases in 2020. About 90% of the 342,000 deaths caused by

cervical cancer occurred in low- and middle-income countries. The highest rates of cervical cancer incidence and mortality are in sub-Saharan Africa (SSA), Central America and South-East Asia. Regional differences in the cervical cancer burden are related to inequalities in access to vaccination, screening and treatment services, risk factors including HIV prevalence, and social and economic determinants such as sex, gender biases and poverty.[8] In Bangladesh, cervical cancer is the second most common cancer of females (12%). The number of new cases was 8,068 (10.6 per 100,000 women) and deaths was 5.214 (7.1 per 100,00 women) in 2018.[9] The prediction was that without any intervention a total of 505,703 women in Bangladesh will die from cervical cancer by the year 2070 and the number will rise to 1,042,859 by 2120.[10]
For cervical cancer screening, women are referred to colposcopy for diagnosis and management. Typically, colposcopy results are characterized by a colposcopic impression and by selection of the worst-appearing site for biopsy.[11] The biopsy result determines whether treatment is required by excision of the transformation zone. In addition, women with persistent abnormalities after colposcopy and women undergoing surveillance after treatment are managed with colposcopy.[12]

Current research works on employing artificial intelligence models for colposcopy evaluation addresses the need for an automated system to aid practitioners in diagnosing cervical cancer and to provide proper treatment in low resource settings [13]. Such automated systems focus on tasks such as improvement of cervix image quality, regional segmentation, identification of unstable regions, transformation zone type classification (TZ) and cancer risk classification [14]. For classification tasks, CNN, SVM classifier, Transfer Learning, Ensemble Learning methods [14][16][17] and for regional segmentation tasks, logical algorithms, Mask-R CNN, UNet, Yolo models are mostly employed in present studies [13][15][18].
Datasets used in current works are mostly collected from local hospitals and annotated by medical professionals, as publicly available datasets are scarce and without proper cancer diagnosis annotation [19]. In present studies, there is a lack of validation of proposed models on datasets from different facilities and regions. This imposes a question on the generalizability of the proposed models and their diagnostic efficiency in clinical use with diversified data.
Our research aims to address this generalizability of cervical cancer classifier AI models where datasets from different facilities are evaluated, and proper domain adaptations are employed for improving the diagnostic performance of the models on a diverse range of data.

- **Objectives:** The primary objective is to curate a comprehensive dataset of colposcopy images sourced from publicly available domains and local health facilities, encompassing a diverse representation of patient demographics, geographic locations, and equipment variations. Building upon this dataset, we seek to develop a robust artificial intelligence model capable of automated classification of transformation zones and detection of cervical cancer within colposcopy images.

  The specific objectives of the study are:

a) Evaluate the artificial intelligence model's performance through clinical validation using a diverse dataset. Measure sensitivity, specificity, and accuracy in classifying cancer stages and identifying the transformation zone in colposcopy images.
b) Assess the usability of the developed model by involving healthcare professionals in the evaluation process. Measure the ease of integration into existing clinical workflows, interpretability of results, and the time efficiency of the model in aiding colposcopy examinations.
c) Investigate the impact of the artificial intelligence model on early detection of cervical cancer. Analyze how the model contributes to identifying precancerous lesions and transformation zones at an earlier stage, potentially leading to improved patient outcomes.
d) Evaluate the model's generalizability across diverse datasets, including local data sources. Measure the performance on data from different regions and healthcare settings to ensure the model's applicability in various clinical scenarios.
e) Investigate the impact of the deep learning model on patient outcomes, such as reduced time to diagnosis, increased accuracy in identifying cancer stages, and improved treatment planning. Assess the potential positive effects on patient well-being and satisfaction
f) Evaluate the model as a clinical decision support tool. Measure its effectiveness in aiding healthcare professionals in making informed decisions during colposcopy examinations, ultimately contributing to more accurate diagnoses and treatment plans.

- **Rationale:** The existing challenges in cervical cancer screening in developing countries like Bangladesh stem from the inherent inaccuracies associated with vision screening methods and the scarcity of trained personnel for comprehensive colposcopic examinations.[21]
  Vision screening, although a common initial approach in resource-limited settings, is marked by a high rate of false negatives and positives, leading to potential delays in the identification of cervical abnormalities or unnecessary distress for patients. Moreover, the shortage of skilled healthcare professionals capable of conducting colposcopic examinations further compounds the problem, limiting the reach and efficacy of cervical cancer screening programs.
  This research aims to bridge these critical gaps by using deep learning for the automated detection of cervical cancer in colposcopy images. The development of a sophisticated deep learning model holds the potential to revolutionize cervical cancer screening in low-income countries. By leveraging a diverse dataset collected from various health facilities within these regions, the model will be trained to accurately identify transformation zones and detect signs of cervical abnormalities with a level of precision that surpasses traditional vision screening methods.
  The significance of this research lies in its potential to provide an accessible and cost-effective solution for cervical cancer screening. The automation of image analysis through a deep learning model mitigates the dependence on human expertise, addressing the shortage of skilled personnel in resource-limited environments. This approach not only enhances the accuracy of detection but also facilitates the scalability of cervical cancer screening initiatives, making them more feasible and sustainable in the face of constrained healthcare resources.

- **Methodology:** In the clinic-based approach for colposcopic cervical cancer screening data collection, information will be directly obtained from patients within healthcare facilities to develop an AI algorithm for automatic cancer detection. The process involves capturing necessary metadata and clinical details, including colposcopic images. Utilizing clinic resources, the collected data will be utilized to train the AI algorithm, providing insights into the likelihood of abnormal findings during the screening. Importantly, the methodology prioritizes privacy by excluding personally identifiable information in the clinic-based data collection process.

    a) **Study Population:** The study is structured as a prospective and retrospective case-controlled investigation aimed at developing and evaluating an AI-based diagnostic tool for the detection of cervical cancer by visual inspection. The target patient groups will consist of confirmed cervical cancer patients diagnosed through gold standard tests and individuals presenting with cervical abnormalities resembling cancer (such as cervical dysplasia, human papillomavirus infection, or other precancerous lesions), with corresponding confirmatory test results. Additionally, data from individuals with suspected cervical cancer (test status unknown) or normal cervical condition will be included to facilitate unsupervised learning. The primary objective is to evaluate the algorithm's capability to differentiate between these categories of patients through the analysis of their medical image data.

        - **Inclusion criteria:**
            - Female patients of age 18 years or older can be selected as subjects.
            - Individuals willing to participate in cervical cancer screening.
            - Availability for colposcopic examination.
            - Women with no history of hysterectomy (total removal of the uterus).
            - Women with no current or prior diagnosis of cervical cancer.
            - Availability of relevant medical records for confirmation and comparison purposes.
        - **Exclusion criteria:**
            - Pregnant women, given the potential impact on screening results and the need for special considerations during pregnancy.
            - Individuals with severe medical conditions or circumstances that may make colposcopic examination inappropriate or unsafe.
            - Patients with conditions that could interfere with the accuracy of the screening results, such as severe vaginal bleeding.
            - Follow-up screenings.

    b) **Sample size calculation:** Following the methodology of sample size calculation to evaluate diagnostic performance (for algorithms in this

case), we use the following method of calculation for a target sensitivity and specificity incorporating disease prevalence [22]:

$$N_{sen} \geq \frac{Z^2{}_{(1-\alpha)/2} \times sen\,(1-sen)}{c^2 \times p}$$

$$N_{spec} \geq \frac{Z^2{}_{(1-\alpha)/2} \times spec\,(1-spec)}{c^2 \times (1-p)}$$

where,

N_{sen}	=	Required sample size for sensitivity, sen
N_{spec}	=	Required sample size for specificity, $spec$
α	=	Confidence level
$Z^2{}_{(1-\alpha)/2}$	=	The Z-score for the confidence level α
p	=	Prevalence of cervical cancer
c	=	Confidence interval
sen	=	Estimated sensitivity
$spec$	=	Estimated specificity

The final sample size N is calculated based on the larger of the two values N_{sen} and N_{spec}. In this study, as we are using deep learning techniques, we need the medical image samples to reflect the various cancerous, precancerous and normal cases. For our analysis, we assume an 80% confidence level ($\alpha = 0.80$) and prevalence of cervical cancer for self-reported instances, $p = 0.261$ [23]. A confidence interval of 5% is selected ($c = 0.05$). We estimate the sensitivity and specificity of our algorithms to be at 75% ($sen = 0.75$ and $spec = 0.75$). Using these values, we obtain the sample size values: $N_{sen} = 471$ and $N_{spec} = 166$. Since $N_{sen} > N_{spec}$, the final sample size for the study will be:

$$N = N_{sen} = 471$$

We can set a target of $N = 500$.

c) **Procedures:** In the prospective phase of the study, data collection will be conducted within clinical settings. Eligible patients will be approached during clinic visits and presented with a consent form for their consideration. Upon agreement, a unique identifier will be assigned to maintain data integrity while preserving patient anonymity. Following the consent process, patients will provide essential clinical information. Healthcare professionals will administer colposcopic examinations, and images of the cervical region will be captured using specialized equipment available in the clinic. This approach ensures the acquisition of non-identifiable information, unique data identifiers, and informed consent directly within the clinical setting, aligning with the specific requirements of colposcopic cervical cancer screening.

In the retrospective phase of the study, additional data will be extracted from the clinic's database of previous screenings. Given the retrospective nature of this approach, tracking down and obtaining consent from individual patients is not feasible. To address privacy concerns, any personally identifiable patient information will be systematically removed from the collected data. This strategy ensures compliance with privacy standards while utilizing valuable information from previous screenings. Although informed consent cannot be obtained for this specific dataset, the study will strictly adhere to ethical guidelines and prioritize patient privacy throughout the data extraction process from the clinic's database.

d) **Methods of Data Collection:** The following fields will be recorded in the data collection for this case-control study:
   - Patient ID (unique identification number)
   - Date & Time of the data input
   - Age
   - Patient's colposcopic image (can be multiple images from different stages of test – normal, acetic acid, iodine etc.)
   - HPV status
   - Transformation zone type
   - Lesion size
   - Provisional diagnosis
   - Suggested management (e.g. routine screening, biopsy etc.)
   - Histopathology
   - Patient's relevant medical/surgical history

   The following information will also be collected if available:
   - Relevant diagnostic test results
   - Swede score

   The cervix images collected from colposcopic assessment of the subjects along with the relevant metadata will immensely benefit in designing the algorithms and analysis of the images. The standard test status and the corresponding result will be used as the ground truth for our detection algorithm.

e) **Data Interpretation:** Upon the conclusion of data collection, exploratory data analysis will be initiated to examine the distribution of patients across various parameters such as transformation zone type, histopathology and relevant clinical factors. Following this, a balanced dataset will be curated, ensuring an equitable representation of image samples.

   This dataset will form the basis for training and evaluating the artificial intelligence (AI) algorithm developed for the automatic classification and detection of abnormalities in colposcopic cervical screening cases. The trained model will provide predictions on the presence or absence of abnormalities in the cervical images.

   To validate the accuracy and clinical relevance of the algorithm's predictions, the results will undergo verification and analysis in collaboration with expert colposcopists. Their input will be

instrumental in refining the automatic algorithm, enhancing its precision in the classification and detection of potential abnormalities during colposcopic cervical cancer screenings.

f) **Statistical Analysis:** Upon dataset availability, statistical analysis will focus on assessing the performance of the developed artificial intelligence algorithms for automatic classification and detection of abnormalities in colposcopic cervical screening cases. Utilizing metrics such as sensitivity, specificity, precision, recall, F-1 score, and overall accuracy, the algorithms will be rigorously evaluated. To ensure robust results, experiments with n-fold cross-validation will be conducted, and mean values along with standard deviations of performance metrics will be calculated. The analysis will culminate in a comparative assessment of different deep learning models, gauged for their effectiveness in the automatic classification task.

Utilization of Results: The study results will play a crucial role in the development and evaluation of an automatic detection algorithm for cervical cancer screening. The algorithm's primary objectives are:

a) Automatic Detection: Assess and identify potential abnormalities in colposcopic images, providing an automated screening tool for efficient detection of cervical cancer risk.

b) Clinical Decision Support: Assist healthcare professionals by offering an automated analysis that aids in prioritizing treatment strategies and making effective clinical decisions based on the algorithm's findings.

c) Systematic Data Storage: Facilitate systematic storage of colposcopic images and relevant metadata to support ongoing research initiatives, all while ensuring the privacy of individuals during the automatic detection process.

These outcomes are poised to significantly enhance the efficiency and accuracy of cervical cancer screening, providing valuable support to healthcare professionals in Bangladesh.

- **Facilities:** In the case of collecting data from colposcopic cervical cancer screening, no additional facilities are required except those the clinics are already equipped with (e.g. image acquisition and data storage capacity).
- **Approval / Forwarding of the Head of Department / Institute / IRB.**
  A forwarding letter from the Department of Biomedical Engineering, Bangladesh University of Engineering and Technology (BUET) is attached.

- **Flow Chart:** The data collection activity and the corresponding timeline is described in the Gantt chart below:

No.	Work/Activities	Months			
		1	2	3	4
1	Initial algorithm with publicly available data				
2	Collection of images and metadata				
3	Homogenization and organization of data				
3	Data processing and analysis				

- **Ethical Implications:** The proposed retrospective/prospective case-control study based on medical records is designed to develop and evaluate the diagnostic performance of Artificial Intelligence (AI) algorithms that will detect cervical cancer stage from colposcopic images. The study poses minimal risk to the subjects according to the HHS (USA) definition.

- **References:**

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PART - C

INFORMED CONSENT FORM (PROSPECTIVE STUDY)

Title: Development and Evaluation of an Artificial Intelligence Model for Cervical Cancer Detection from Colposcopic Images

Principal Investigator:

Dr. Taufiq Hasan, Associate Professor,
Department of Biomedical Engineering, BUET, Dhaka – 1205

Please check all that are applicable:

☐ I am an adult participant in this study.

☐ I am the parent or guardian granting permission for a child in this study (the use of "you" refers to "your child" or "your ward.")

Are you participating in any other research studies? (Yes/No) _____

PURPOSE OF PROJECT

You are invited to participate in a project entitled **Development and Evaluation of an Artificial Intelligence Model for Cervical Cancer Detection from Colposcopic Images.** This project focuses on developing an algorithm that will automatically detect cervical cancer or precancerous stages using colposcopy images. The period of the study will be between November 1, 2023 to January 31, 2024. You are selected as a possible participant in the study.

If you decide to terminate your participation in this study, you should notify Dr. Taufiq Hasan at +8801817579844.

PROCEDURES

The clinic-based approach involves directly obtaining information during clinical visits for developing an automatic cancer detection AI algorithm. No personally identifiable data is collected, ensuring privacy. Eligible female patients (age 18 or older) without prior cervical cancer diagnosis will provide essential clinical information during colposcopic examinations. In the retrospective phase, data from previous screenings will be extracted, ensuring privacy standards. The recorded data includes patient ID, colposcopic images, HPV status, and relevant medical history. The collected dataset will train the AI algorithm for automatic classification and detection, emphasizing patient privacy throughout the process.

THE PROCEDURE IS MINIMALLY INVASIVE

The data collected during these sessions will be put into one of the databases of the Department of BME, BUET and will be used for future research.

No traditionally used identifying information about you, such as your name, address, telephone number, or national ID number, will be put into the public database. Your privacy is very important to us, and we will use safety measures to protect it. Despite all the safety measures that we will use, we cannot guarantee that your identity will never become known.

PARTICIPANT RESPONSIBILITIES

As a participant, your responsibilities include:

- Adhere to instructions provided by healthcare professionals during clinic visits for data collection.
- Contact the data collection coordinator or research study staff promptly if you have any questions or concerns.
- If you are a healthcare professional, particularly a colposcopist, ensure accurate maintenance of the image ID to prevent data mix-ups.
- Notify the coordinator or research staff directly if you decide to withdraw from the study on the clinic-based system, ensuring seamless communication with the study staff.

WITHDRAWAL FROM STUDY

If you first agree to participate and then you change your mind, you are free to withdraw your consent and discontinue your participation at any time.

If you decide to withdraw your consent to participate in this study, you can directly inform Dr. Taufiq Hasan at +8801817579844 or notify the study staff.

If you withdraw from the study for any reason all the data acquired from you will be removed from the databases.

YOU MUST NOTIFY ABOUT YOUR DISSENT WITHIN THE PERIOD OF THE STUDY BEING CONDUCTED.

The Protocol Director may also withdraw you from the study without your consent for one or more of the following reasons:

- Failure to follow the instructions during data collection.
- The Protocol Director decides that continuing your participation could be harmful to you.
- You need other treatments that are not allowed in the study.
- The study is canceled.
- Unanticipated circumstances.
- Other administrative reasons.

POSSIBLE RISKS, DISCOMFORTS, AND INCONVENIENCES

There may be mild discomfort during the procedure and, in rare cases, minimal bleeding or infection at the biopsy site. You should contact the Protocol Director or the study staff if you have any questions.

POTENTIAL BENEFITS

We cannot and do not guarantee or promise that you will receive any benefits from this study. The study is being conducted for humanitarian purposes, which envision a long-term goal that will benefit patients suffering from or at the risk of having cervical cancer.

PARTICIPANT'S RIGHTS

You should not feel obligated to agree to participate. Your questions should be answered clearly and to your satisfaction. If you decide not to participate, notify the project coordinator or the study staff.

CONFIDENTIALITY

The results of this research study may be presented at scientific or medical meetings or published in scientific journals. Your identity and/or your personal health information will not be disclosed except as authorized by you or as required by law**.**

CONTACT INFORMATION

Questions, Concerns, or Complaints: If you have any questions, concerns or complaints about this research study, its procedures, risks and benefits, or alternative courses of treatment, you should ask the data collection coordinator, **Dr. Taufiq Hasan**. You should also contact him at any time if you feel you have been harmed by being a part of this study at **+8801817579844.**

May we contact you about future studies that may be of your interest? (Yes/No)

Checking on the box with a click means you agree to be in this study.

☐ Agreed

JUSTIFICATIONS FOR INFORMED CONSENT WAIVER (RETROSPECTIVE STUDY)

The proposed research is a case-control study that only uses medical records of colposcopy. As the number of samples required is large (500 according to our sample size calculation) compared to the monthly recorded cases, it is not possible to return to the patients for acquiring their consent in case of previously recorded data. Considering the high potential impact of the study, we earnestly request waiver of informed consent. The justifications for this request is provided below:

1. On the topic of informed consent waiver, the regulatory authority of the United States, Department of Health and Human Services (HHS) mentions in 45 C.F.R. § 46.116(d):

   > "*An IRB may approve a consent procedure which does not include, or which alters, some or all of the elements of informed consent set forth in this section, or waive the requirements to obtain informed consent provided the IRB finds and documents that:*
   >
   > *(1) The research involves no more than minimal risk to the subjects;*
   >
   > *(2) The waiver or alteration will not adversely affect the rights and welfare of the subjects;*
   >
   > *(3) The research could not practicably be carried out without the waiver or alteration; …*"

2. On the topic of case control studies, the Bangladesh Medical Research Council (BMRC) "Ethical Guidelines for Conducting Research Studies Involving Human Subjects" mentions on Page 45:

   > "*However, if it entails only a review of medical records, informed consent may not be required and indeed may very often not be feasible*".

In light of the abovementioned regulatory guidelines described by HHS (USA) and BMRC, we want to highlight that our study fulfills all of the above conditions as explained below:

1. The proposed research involves no more than minimal risk to subjects. According to HHS document 45 C.F.R. § 46.102(i):

   > "*Minimal risk means that the probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests.*"

   We will use de-identified medical records for the study. This falls into the category of minimal risk as described above.

2. The research could not be carried out practicably without the waiver or alteration. Training artificial intelligence algorithms require a huge amount of data from a large number of patients due to the overfitting problem (further detailed in the sample size calculation section below). It is not practically possible to collect signed or verbal informed consent from each patient from each hospital. In addition, most of the patients hospitalized due to COVID-19 are in severe conditions and are not capable of providing consent.
3. The waiver or alteration will not adversely affect the rights and welfare of the subjects. Only their digital medical images and clinical history data will be used for the research. Personal identifying information (name, etc.) will be removed at the source.

With the explanations provided above, we hope that the ethical review committee will be kind enough to approve our request to waive the informed consent requirement for this case-control study using medical records. As we have mentioned above, the study is of potentially high impact and unfortunately not feasible without the waiver.