Prospective, Multi-Center, Randomized Controlled Trial for Skeletal Age Assessment AI Model

Study Protocol and Statistical Analysis Plan

NCT03530098

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Clinical Research Protocol
SKELETAL AGE ASSESSMENT AI MODEL

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Investigational Device:	Skeletal age assessment AI model
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Medical Monitor:	N/A
Coordinating Center:	Stanford University

PROTOCOL SYNOPSIS

TITLE	Prospective, Multi-Center, Randomized Controlled Trial for Skeletal Age Assessment AI Model
SPONSOR	N/A
FUNDING ORGANIZATION	N/A
NUMBER OF SITES	6
RATIONALE	To determine whether the AI model improves radiologist performance.
STUDY DESIGN	This is a prospective, multi-center, randomized controlled trial with two arms: Experiment and Control. Radiologists receive the AI model for studies randomized into the Experiment arm before dictating a final impression.
PRIMARY OBJECTIVE	To determine whether radiologists are more accurate at assessing skeletal age using the AI model, compared to not using the AI model.
SECONDARY OBJECTIVES	To determine whether radiologists are more efficient at assessing skeletal age using the AI model, compared to not using the AI model.
NUMBER OF SUBJECTS	1600 interpretations by consented radiologists.
SUBJECT SELECTION CRITERIA	Inclusion Criteria: 1. Verbal informed consent obtained from interpreting radiologist. 2. Procedure code or study description indicative of hand radiograph for skeletal age assessment. Exclusion Criteria: 1. Trainee provided a preliminary interpretation.
TEST DEVICE, DEPLOYMENT	The AI model will populate the radiologists' report templates.
CONTROL DEVICE, DEPLOYMENT	The AI model will not populate the radiologists' report templates.
DURATION OF STUDY	Estimated to be 6 months from the start date.
CONCOMMITANT MEDICATIONS	N/A
EFFICACY EVALUATIONS	N/A

PRIMARY ENDPOINT	• Mean absolute difference between dictated final impressions and the consensus determination of a panel of radiologists.
SECONDARY ENDPOINTS	• Radiologist interpretation time.
OTHER EVALUATIONS	N/A
SAFETY EVALUATIONS	Since the device does not pose greater than minimal risk, neither an adverse event (AE) or serious adverse experience (SAE) is expected. Unanticipated risks will be reported to the IRB, in accordance with IRB standards.
PLANNED INTERIM ANALYSES	N/A
STATISTICS **Primary Analysis Plan**	1. Detect differences in the primary endpoint between Experiment and Control arms, using a two-sided Student t-test. 2. Detect differences in the secondary endpoint between Experiment and Control arms, using a Wilcoxon rank-sum test.
Rationale for Number of Subjects	Targeting a power of 0.75, statistical tests achieved a power of 0.79 to detect a difference of 0.50 months for 1600 interpretations.

1 BACKGROUND

Radiologists perform a skeletal age assessment to determine the developmental status of a pediatric patient. We trained an AI model on the open-source RSNA dataset to predict the skeletal age from a hand radiograph and intend to determine the effect of its clinical use in a prospective, multi-center, randomized controlled trial.

1.1 Overview of Non-Clinical Studies

Previous work from Larson, et al. [1] suggests that using an AI model as a diagnostic aid could improve the quality of skeletal age assessment.

[1] Larson, et al. "Performance of a Deep-Learning Neural Network Model in Assessing Skeletal Maturity on Pediatric Hand Radiographs" (2017).

1.2 Overview of Clinical Studies

To our knowledge, there do not exist previous clinical studies in the form of a prospective clinical trial of any AI model.

2 STUDY RATIONALE

Though the AI model from Larson, et al. [1] performs as well as human radiologists in controlled settings, it remains uncertain whether use of an AI model as a diagnostic aid can improve the quality of skeletal age assessment in true clinical settings.

3 STUDY OBJECTIVES

3.1 Primary Objective

The primary objective is to determine the effect of using an AI model as a diagnostic aid for skeletal age assessment on the quality of radiologists' interpretations, as measured by the mean absolute difference between their dictated final impressions and the consensus determination of a panel of radiologists.

3.2 Secondary Objectives

The secondary objective is to determine the effect of using an AI model as a diagnostic aid for skeletal age assessment on the efficiency of radiologists' interpretations, as measured by their interpretation times.

4 STUDY DESIGN

4.1 Study Overview

This is a prospective, multi-center, randomized controlled trial. 1600 interpretations by consented radiologists are planned.

Each of the interpreted studies will be assigned at random to one of two arms: Experiment or Control. The AI model will populate the radiologists' report templates for studies assigned to the Experiment arm. The AI model will not populate the radiologists' report templates for studies assigned to the Control arm.

5 CRITERIA FOR EVALUATION

5.1 Primary Efficacy Endpoint

The primary endpoint is mean absolute difference between dictated final impressions and the consensus determination of a panel of radiologists.

5.2 Secondary Efficacy Endpoints

- Radiologist interpretation time.

5.3 Safety Evaluations

- Since the device does not pose greater than minimal risk, neither an adverse event (AE) or serious adverse experience (SAE) is expected. Unanticipated risks will be reported to the IRB, in accordance with IRB standards.

6 SUBJECT SELECTION

6.1 Study Population

Radiologists who interpret hand radiographs for skeletal age assessment will be eligible for participation in this study. Studies that meet the inclusion and exclusion criteria will be eligible for this study.

6.2 Inclusion Criteria

1. Verbal informed consent obtained from interpreting radiologist.
2. Procedure code or study description indicative of hand radiograph for skeletal age assessment.

6.3 Exclusion Criteria

1. Trainee provided a preliminary interpretation.

7 CONCURRENT MEDICATIONS

The study does not involve medications or chronic therapies.

8 STUDY TREATMENTS

8.1 Method of Assigning Subjects to Treatment Groups

Studies will be assigned at random to Experiment or Control treatment groups in a 1:1 ratio using the Python random package.

8.2 Blinding

Due to the objectives of the study, the identity of Experiment and Control treatment groups will be known to radiologists.

8.3 Formulation of Test and Control Products

The study does not involve test or control devices. The Control arm represents the absence of any intervention and is consistent with the current standard of care.

8.4 Supply of Study Device at the Site

The device will be installed at the investigational sites one time prior to randomization by the Investigator. The device will receive studies from the sites, perform randomization, and populate the radiologists' report templates for studies assigned to the Experiment arm for the duration of the study.

9 STUDY PROCEDURES AND GUIDELINES

A Schedule of Events representing the required testing procedures to be performed for the duration of the study is diagrammed in Appendix 1.

Prior to conducting any study-related activities, verbal informed consent must be obtained from the radiologist. In addition, written informed consent by the patient must be waived by the IRB.

9.1 Clinical Assessments

9.1.1 Concomitant Medications

The study does not require documentation of concomitant medication or concurrent therapies.

9.1.2 Demographics

Demographic information (date of birth, gender, race) will be collected retrospectively.

9.1.3 Medical History

Relevant medical history, including history of current disease, other pertinent history, and information regarding underlying diseases will be collected retrospectively.

9.1.4 Physical Examination

The study does not require a physical examination.

9.1.5 Vital Signs

The study does not require body temperature, blood pressure, pulse and respirations.

9.1.6 Adverse Events

Since the device does not pose greater than minimal risk, neither an adverse event (AE) or serious adverse experience (SAE) is expected. Unanticipated risks will be reported to the IRB, in accordance with IRB standards.

9.2 Clinical Laboratory Measurements

The study does not require clinical laboratory measurements.

10 EVALUATIONS BY VISIT

The device records individual visits.

1. Receive the study as a DICOM file.
2. Record the study as a DICOM file.
3. Randomizes the study.
4. Perform and record the AI model.
5. If randomized into the Experiment arm, populate the radiologists' report template with the AI model.

11 ADVERSE EXPERIENCE REPORTING AND DOCUMENTATION

11.1 Adverse Events

An adverse event (AE) is any untoward medical occurrence in a clinical investigation of a patient administered a pharmaceutical product and that does not necessarily have a causal relationship with the treatment. An AE is therefore any unfavorable and unintended sign (including an abnormal laboratory finding), symptom or disease temporally associated with the administration of an investigational product, whether or not related to that investigational product.

The device is not a pharmaceutical product.

Since the device does not pose greater than minimal risk, an adverse event (AE) is not expected. Unanticipated risks will be reported to the IRB, in accordance with IRB standards.

11.2 Serious Adverse Experiences (SAE)

An SAE is defined as any AE occurring at any dose that results in any of the following outcomes:

- death
- a life-threatening adverse experience
- inpatient hospitalization or prolongation of existing hospitalization
- a persistent or significant disability/incapacity
- a congenital anomaly/birth defect

Other important medical events may also be considered an SAE when, based on appropriate medical judgment, they jeopardize the subject or require intervention to prevent one of the outcomes listed.

The device is not a pharmaceutical product.

Since the device does not pose greater than minimal risk, a serious adverse experience (SAE) is not expected. Unanticipated risks will be reported to the IRB, in accordance with IRB standards.

12 DISCONTINUATION AND REPLACEMENT OF SUBJECTS

12.1 Early Discontinuation of Study Device

A radiologist may be discontinued from study treatment at any time if the radiologist or the Investigator feels that it is not in the radiologist's best interest to continue.

All radiologists are free to withdraw from participation at any time, for any reason, specified or unspecified, and without prejudice.

Reasonable attempts will be made by the Investigator to provide a reason for radiologist withdrawals.

12.3 Withdrawal of Subjects from the Study

A radiologist may be withdrawn from the study at any time if the radiologist or the Investigator feels that it is not in the radiologist's best interest to continue.

All radiologists are free to withdraw from participation at any time, for any reason, specified or unspecified, and without prejudice.

Reasonable attempts will be made by the Investigator to provide a reason for radiologist withdrawals.

12.4 Replacement of Subjects

Radiologists who withdraw from the study treatment will not be replaced.

Radiologists who withdraw from the study will not be replaced.

13 PROTOCOL VIOLATIONS

A protocol violation occurs when the radiologist or Investigator fails to adhere to significant protocol requirements affecting the inclusion, exclusion, radiologist safety and primary endpoint criteria. Protocol violations for this study include, but are not limited to, the following:

- Failure to meet inclusion/exclusion criteria

Failure to comply with Good Clinical Practice (GCP) guidelines will also result in a protocol violation. The Investigator will determine if a protocol violation will result in withdrawal of a radiologist.

When a protocol violation occurs, it will be discussed with the Investigator and a Protocol Violation Form detailing the violation will be generated.

14 STATISTICAL METHODS AND CONSIDERATIONS

14.1 Data Sets Analyzed

Studies that meet the inclusion and exclusion criteria will be included the analysis.

14.2 Demographic and Baseline Characteristics

The following demographic variables will be summarized: age, sex, skeletal age, and clinical histories.

14.3 Analysis of Primary Endpoint

Two-sided Student's t-test will be employed for the primary endpoint.

14.4 Analysis of Secondary Endpoints

Wilcoxon rank-sum test will be employed for the secondary endpoint.

14.5 Interim Analysis

There is no planned interim analysis.

14.6 Sample Size and Randomization

Targeting a power of 0.75, statistical tests achieved a power of 0.79 to detect a difference of 0.50 months for 1600 interpretations.

15 DATA COLLECTION, RETENTION AND MONITORING

15.1 Data Collection Instruments

The Investigator will prepare and maintain adequate and accurate documents designed to record all observations and other pertinent data for each radiologist.

The Investigator is responsible for all information collected on radiologists enrolled in this study. All data collected during the course of this study must be reviewed and verified for completeness and accuracy by the Investigator.

15.2 Data Management Procedures

The data will be entered into a validated database. The Investigator will be responsible for data processing, in accordance with procedural documentation.

All procedures for the handling and analysis of data will be conducted using good computing practices.

15.3 Data Quality Control and Reporting

After data have been entered into the study database, a system of computerized data validation checks will be implemented and applied to the database on a regular basis. The study database will be updated in accordance with the resolved queries. All changes to the study database will be documented.

15.4 Archival of Data

The database is safeguarded against unauthorized access by established security procedures; appropriate backup copies of the database and related software files will be maintained. Databases are backed up by the database administrator in conjunction with any updates or changes to the database.

At critical junctures of the protocol (e.g., production of interim reports and final reports), data for analysis is locked and cleaned per established procedures.

15.5 Availability and Retention of Investigational Records

The Investigator must make study data accessible to the IRB/IEC and Regulatory Agency (e.g., FDA) inspectors upon request.

All study documents must be kept secured for a period of two years following conclusion of the study.

15.6 Monitoring

The study does not involve monitoring by representatives of a Sponsor.

16 ADMINISTRATIVE, ETHICAL, REGULATORY CONSIDERATIONS

The study will be conducted according to the Declaration of Helsinki, Protection of Human Volunteers (21 CFR 50), Institutional Review Boards (21 CFR 56), and Obligations of Clinical Investigators (21 CFR 312).

To maintain confidentiality, all laboratory specimens, evaluation forms, reports and other records will be identified by a coded number and initials only. All study records will be kept in a locked file cabinet and code sheets linking a patient's name to a patient identification number will be stored separately in another locked file cabinet. Clinical information will not be released without written permission of the subject, except as necessary for monitoring by the FDA. The Investigator must also comply with all applicable privacy regulations (e.g., Health Insurance Portability and Accountability Act of 1996, EU Data Protection Directive 95/46/EC).

16.1 Protocol Amendments

Any amendment to the protocol will be written by the investigator. Protocol amendments cannot be implemented without prior written IRB/IEC approval except as necessary to eliminate immediate safety hazards to patients. A protocol amendment intended to eliminate an apparent immediate hazard to patients may be implemented immediately, provided the IRBs are notified within five working days.

16.2 Institutional Review Boards and Independent Ethics Committees

The protocol and consent form will be reviewed and approved by the IRB/IEC of each participating center prior to study initiation. Serious adverse experiences regardless of causality will be reported to the IRB/IEC in accordance with the standard operating procedures and policies of the IRB/IEC, and the Investigator will keep the IRB/IEC informed as to the progress of the study. The Investigator will obtain assurance of IRB/IEC compliance with regulations.

Any documents that the IRB/IEC may need to fulfill its responsibilities (such as protocol, protocol amendments, Investigator's Brochure, consent forms, information concerning patient recruitment, payment or compensation procedures, or other pertinent information) will be submitted to the IRB/IEC. The IRB/IECs written unconditional approval of the study protocol and the informed consent form will be in the possession of the Investigator

before the study is initiated. This approval must refer to the study by exact protocol title and number and should identify the documents reviewed and the date of review.

Protocol and/or informed consent modifications or changes may not be initiated without prior written IRB/IEC approval except when necessary to eliminate immediate hazards to the patients or when the change(s) involves only logistical or administrative aspects of the study. Such modifications will be submitted to the IRB/IEC and written verification that the modification was submitted and subsequently approved should be obtained.

The IRB/IEC must be informed of revisions to other documents originally submitted for review; serious and/or unexpected adverse experiences occurring during the study in accordance with the standard operating procedures and policies of the IRB; new information that may affect adversely the safety of the patients of the conduct of the study; an annual update and/or request for re-approval; and when the study has been completed.

16.3 Informed Consent Form

Written informed consent by the patient must be waived by the IRB.

A properly executed, verbal, informed consent will be obtained from each radiologist prior to entering the radiologist into the trial. Information should be given in oral form and radiologists must be given ample opportunity to inquire about details of the study.

16.4 Publications

The publication or presentation of any study results shall comply with all applicable privacy laws, including, but not limited to, the Health Insurance Portability and Accountability Act of 1996.

APPENDIX 1. SCHEDULE OF EVENTS

	REQUIRED
Install Device	**X**
Informed Consent	**X**
Test Device	**X**
Begin Randomization	**X**
End Randomization	**X**
Collect Data from Device	**X**