User Guide

ARDA (Automated Retinal Disease Assessment)

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Contact support

If you're having problems with ARDA, you can contact the Verily Life Sciences LLC support team at:

- Within the United Kingdom: 0800 026 3727 (Toll free number), or arda-success-eu@verily.com.
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- Within India: 00 0800 0402 419, or arda-success-india@verily.com.

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User

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Glossary

Term	Definition
API	Application programming interface
ARDA	Automated retinal disease assessment
DR	Diabetic retinopathy
DME	Diabetic macular edema
ICDR	International Clinical Diabetic Retinopathy
ICO	International Council of Ophthalmology
IFU	Instructions for Use
mtmDR	More than mild diabetic retinopathy
NPDR	Non-proliferative diabetic retinopathy
PDR	Proliferative diabetic retinopathy
UWF	Ultra-widefield
vtDR	Vision-threatening diabetic retinopathy

Table of Contents

ARDA Deployment Guides

This guide is intended to be used in conjunction with other ARDA Instructions for Use (IFUs). The table below explains the various deployment phases, and which IFUs should be used during each phase.

Deployment Phases	**Applicable IFUs**
*This document is applicable for **Phase 1** and **Phase 7***	

Phase 1 Familiarize yourself with ARDA's intended use and capabilities	ARDA User Guide (Doc # 100423), intended for **Healthcare Providers**
Phase 2 Fulfill the prerequisites to integrate with the ARDA APIs, including, but not limited to: obtaining access to Partner Issue Tracker, setting up GCP projects, requesting access to ARDA APIs	ARDA Google Cloud Platform Projects Setup Guide (Doc # 101304), intended for **Technical Support Staff**
Phase 3 Integrate your software with ARDA Ingestion and Diagnosis APIs	ARDA Ingestion & Diagnosis Integration Guide (Doc # 100635), intended for **Technical Support Staff** ARDA DICOM Conformance Statement (Doc # 100462), intended for **Technical Support Staff**
Phase 4 Perform installation qualification to ensure your integration with ARDA Ingestion and Diagnosis APIs was successful	ARDA Ingestion & Diagnosis Integration Guide (Doc # 100635), intended for **Technical Support Staff**
[Optional] Phase 5 Integrate your software with ARDA Medical Imaging Programs API for self-sufficient management of program creation This step may be done in parallel with **Step 3** and **Step 4**; those steps are not prerequisites for this step.	ARDA Medical Imaging Programs Integration Guide (Doc # 101187), intended for **Technical Support Staff**
Phase 6 Provision data silos (Programs) for clinical use. This might include creating new GCP Projects and provisioning new programs. Provisioning of programs will be performed by: ● Interacting with ARDA Medical Imaging Programs API if **[Optional] Step 5** was performed, or ● Requesting a Verily employee provision programs on your behalf by filing a ticket via Partner Issue Tracker if **[Optional] Step 5** was not performed	ARDA Google Cloud Platform Projects Setup Guide (Doc # 101304), intended for **Technical Support Staff**
Phase 7 Use ARDA in clinical environment	ARDA User Guide (Doc # 100423), intended for **Healthcare Providers**

1.0 About this User Guide

The purpose of this User Guide is to describe the Automated Retinal Disease Assessment (ARDA) and provide instructions for its safe and appropriate use.

This document is intended to be used by healthcare providers and their designated staff who will use and interpret the output of the ARDA product.

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- Elsewhere within the European Union: +44 20 76608851, or arda-success-eu@verily.com.
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2.0 Introduction to ARDA

Automated Retinal Disease Assessment (ARDA) provides a real-time and automated evaluation of diabetic retinopathy (DR) and diabetic macular edema (DME) severity based on analysis of fundus or retinal images. With this real-time feedback, healthcare providers can determine whether a patient should get further evaluation and management for DR and/or DME. Primary care providers can refer individuals at higher risk for vision loss for further evaluation by an eye care specialist. Eye care specialists can use the ARDA output as adjunctive information in their interpretation of fundus or retinal images.

The ARDA application programming interface (API) is able to:

- Receive fundus or retinal images
- Run a machine learning algorithm that analyzes the severity of DR and DME based on the fundus or retinal imaging, using the widely accepted International Clinical Diabetic Retinopathy and Diabetic Macular Edema Disease Severity Scale
- Provide the DR and DME grade output to the intended users - healthcare providers who are responsible for making patient management and referral decisions
- Save the patient images for future algorithm improvements if patient informed consent has been obtained

2.1 Intended Use

The *ARDA Software Platform* is machine learning-based software that is intended for the screening, diagnosis and management of ocular diseases. ARDA is part of the ARDA Software Platform.

2.2 Indications for Use

ARDA is intended for screening of:

- Diabetic Retinopathy, and
- Diabetic Macular Edema

in adult (18+) diabetic patients using fundus or retinal photography. ARDA is intended for use by healthcare providers.

2.3 Contraindications

ARDA **should not** be used in patients who meet the following criteria:

- Under 18 years of age
- Pregnant
- Patients with any visual symptoms or conditions (e.g., loss of vision, blurry vision, persistent floaters), other than those corrected with glasses, contact lenses or other refractive corrections
- Previous diagnosis of macular edema, severe non-proliferative diabetic retinopathy, proliferative diabetic retinopathy, radiation retinopathy or retinal vein occlusion (RVO)
- Undergone any laser treatment of the retina in the past
- Undergone any retinal surgeries
- Patients who have not been diagnosed with diabetes mellitus

This is because ARDA has not been tested in these groups and/or the risk of use currently outweighs any possible benefit.

It is recommended that these patients be referred for examination by an eye care specialist.

2.4 User Profiles

See the chart below to learn about the different users who might use and interact with ARDA.

ARDA user profiles	
Healthcare providers	Health professionals who have medical training and/or licensure. Training may include: • fundus or retinal image acquisition training (e.g., camera technician) • healthcare professionals with ophthalmic training (e.g., in conducting eye exams) • general medical training (e.g., primary care physicians) • specialization in diabetes management (e.g., endocrinologists)

	• eye care specialists (e.g., optometrists, ophthalmologists, or retina specialists).
Technical support staff	Technical staff with training in software engineering and experience integrating APIs. Technical support staff will perform integration of ARDA APIs and report any API related issues on behalf of healthcare providers.

2.5 Access to ARDA APIs

In order to access ARDA APIs, your organization must have an appropriate agreement with Verily Life Sciences LLC.

3.0 Warnings and Precautions

WARNING

When selecting a region to store ARDA data, please ensure that you have legal permission to collect and store this type of data; that the data may be stored in the region you have selected; and that the ARDA product is used appropriately under applicable laws.

The user assumes responsibility and liability for any legal consequences that arise from improper use of ARDA.

ARDA is not intended to replace an annual eye examination.

ARDA is intended to be used by or under the supervision of a physician.

ARDA does not provide final patient management or referral recommendations. It is the responsibility of the user interpreting ARDA's output to take into account all available clinical information regarding the patient in determining whether a patient should be referred to an eye care specialist for further evaluation.

ARDA is intended for the screening of DR and DME only. It is not intended for the screening of any other conditions or diseases.

ARDA is intended for the screening DR and DME only. It does not provide a final diagnosis decision.

ARDA is a software device intended for screening of DR and DME. It does not provide any treatment of DR, DME or any other condition.

ARDA should only be used and interpreted by healthcare providers who have read and understood the content in this User Guide, and who understand the device output and the appropriate patient management recommendations.

The ARDA algorithm performs an automated analysis of fundus or retinal images for screening of DR and DME. There are risks that the algorithm may incorrectly identify the DR or DME grade, resulting in either:

- A patient being unnecessarily referred to an eye care specialist when, in fact, the patient may not have a severity of DR or DME that would warrant further evaluation by a specialist.
- A patient not being evaluated by an eye care specialist when, in fact, the

patient may have a severity of DR or DME that would warrant further evaluation by a specialist. **The risk is greater here because it means that someone who should see a specialist won't, so potentially the patient's vision could deteriorate.**

Please consult the Summary of ARDA Performance Evaluation (Section 6.0) in this User Guide for further information regarding the performance of the algorithm.

ARDA should only be used with good quality fundus or retinal images that satisfy the image acceptance criteria noted in this User Guide. Fundus or retinal images submitted to ARDA should be acquired following the instructions of the camera manufacturer for obtaining high quality images.

If a patient consistently receives an output from ARDA of "ungradable," he/she should be referred for evaluation by an eye care specialist according to standard of care.

4.0 Set up the ARDA API

4.1 Hardware and software recommendations

The ARDA application programming interface (API) needs to be integrated with a system (e.g. electronic medical record, image viewer or management system) available at the clinical site. ARDA does not include a graphical user interface (e.g., it is not a mobile app) and does not provide a final patient report. During the installation process, the ARDA API will be integrated into the electronic system of the clinical site, and the clinical site will be responsible for displaying the ARDA output in a format that is consistent with their clinical practice.

ARDA has been validated on the following fundus or retinal cameras as described in the Summary of ARDA Performance Evaluation (Section 6.0):

- Crystalvue NFC-700
- Canon CR-2
- Topcon NW-400
- Optovue iCam
- CenterVue DRS
- Optos P200T

4.2 Install ARDA on your system

Your technical support staff will perform installation of ARDA, according to the ARDA Integration Guide (Doc # 100635) provided separately.

5.0 Use and understand ARDA

5.1 Submit an image to ARDA

Fundus or retinal images taken by a trained retinal photographer according to the camera manufacturer's instructions are uploaded to the ARDA API through a DICOM STOW-RS transfer for analysis of DR and DME severity. A diagnosis request is made for the DICOM study in question and the ARDA API returns results to the user's electronic health system for each image.

5.1.1 Image acceptance criteria

ARDA should only be used with good quality fundus or retinal images that satisfy the image acceptance criteria noted below. Refer to the camera manufacturer's User Guide and/or Instructions for Use for instructions on camera operation and image capture.

The images submitted to the ARDA algorithm for analysis must comply with the following specifications:

Specification	Fundus Images	UWF Retinal Images
Format	Up to 1 image per eye in a single DICOM study.	
Anatomical Field	The primary field of view, where the macula and optic nerve are equally distant from the center of the image.	The macula-centered (central pole) field of view.
Image Resolution	1024x1024 pixels or higher.	4000x4000 pixels or higher.
Field of View	40°—45°	200° (internal degree)
Color	Images must be taken using either 3-channel color (also known as true/natural color images) or white light.	Images must be taken using RG color composite (also known Optomap color)
Miscellaneous	No text may be present *anywhere* (even within the black surrounding mask region) on an image.	

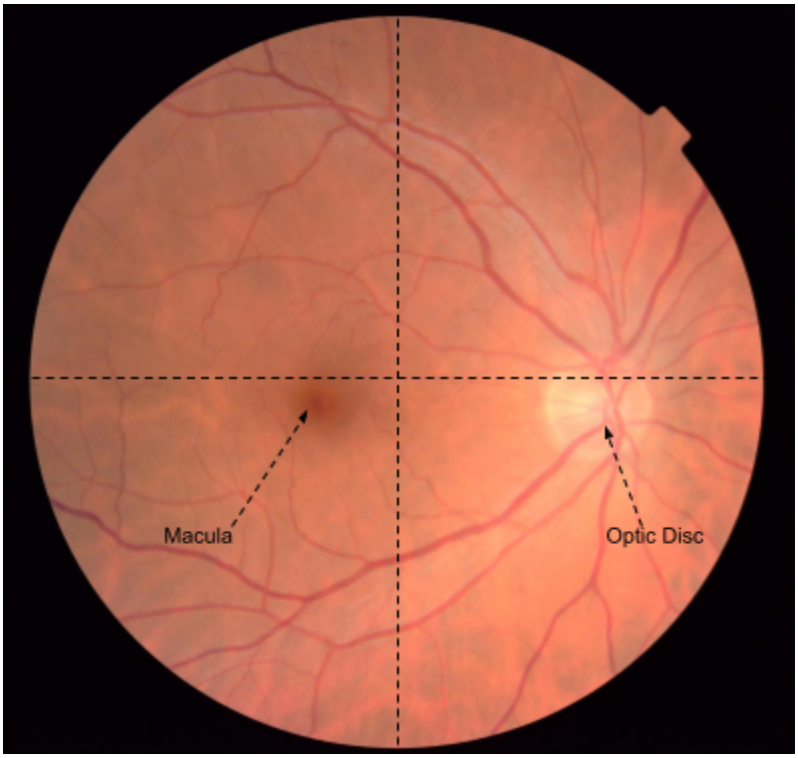
If the images do not meet these specifications, the ARDA algorithm may return the results as "Ungradable," or an error may occur.

5.1.2 Examples of fundus and retinal images

Below are a few examples of fundus and retinal images to help you better understand what qualifies as an acceptable image for analysis by ARDA.

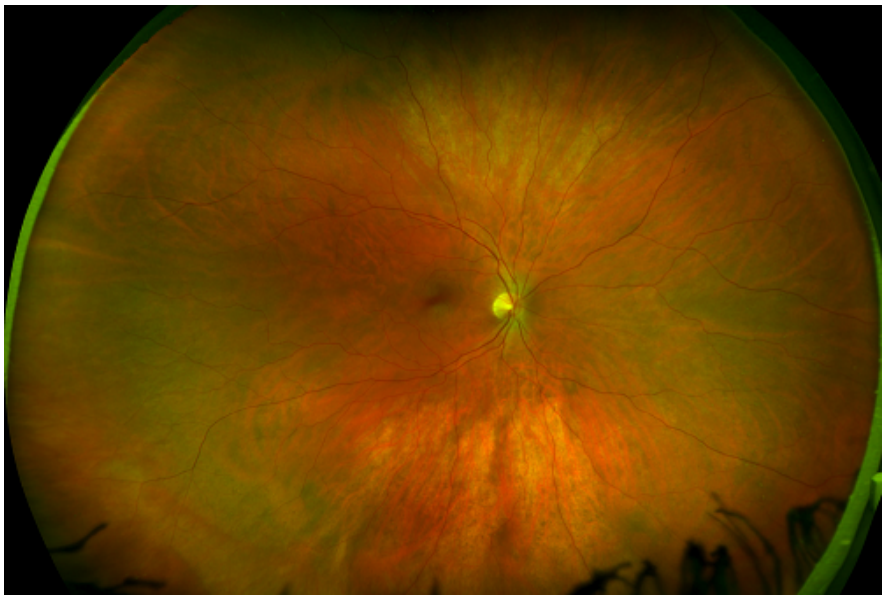
Example of a fundus image that is acceptable

The image below is an example of an image that meets the ARDA image acceptance criteria because it is of the primary field, with a 45° field of view, taken in natural colors, and does not include any text. *(Note: For space considerations in this document, this example image is smaller than 1024x1024 pixels).*



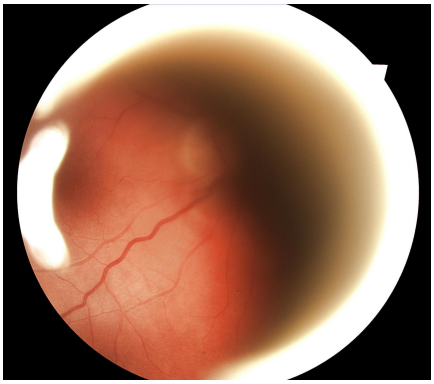
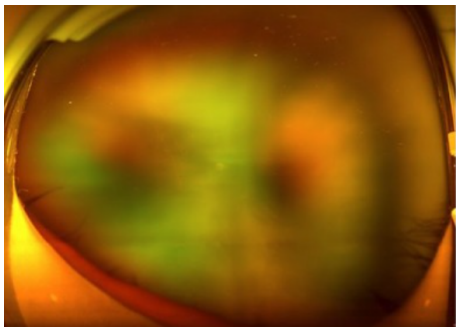
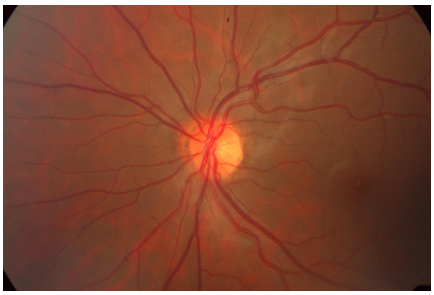
Example of a retinal image that is acceptable

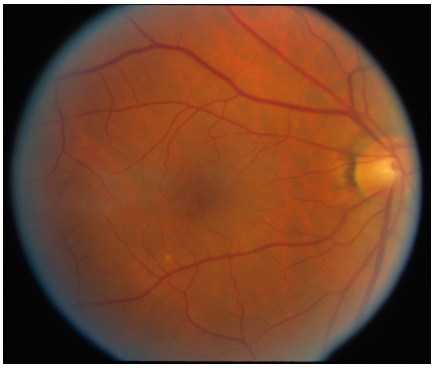
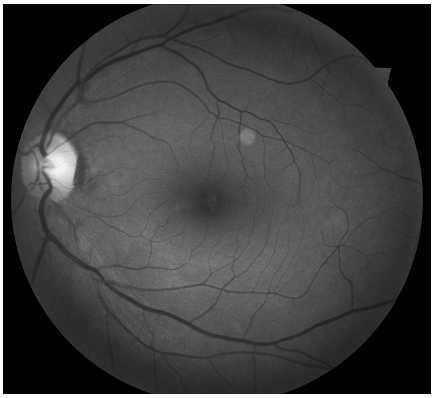
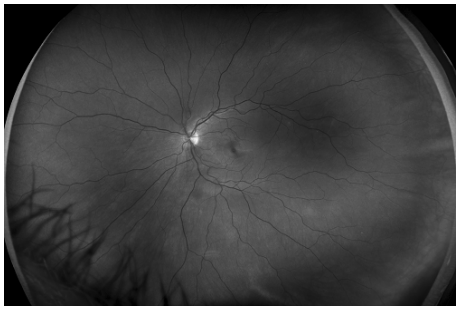
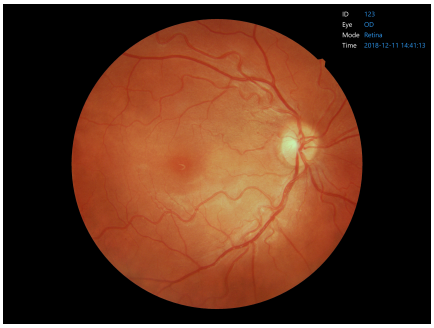
The image below is an example of an image that meets the ARDA image acceptance criteria because it is of the macula field, with a 200° field of view, taken in Red-Green color composite, and does not include any text. *(Note: For space considerations in this document, this example image is smaller than 4000x4000 pixels).*



Examples of fundus and retinal images that are not acceptable

See the table and images below for examples of why an image may not be gradable:

Description of Issue	Fundus Image Example	UWF Retinal Image Example
Artifacts in the image An image with significant artifacts. The ARDA algorithm does not accept images with significant artifacts (e.g., as a result of patient misalignment, sub-optimal focus, overexposure, etc.)		
Incompatible field An unsupported field of the retina. This example is centered at the optic disc, however the ARDA algorithm analyzes fundus images from the primary field and UWF retinal images of the macula centered field.		Not Applicable

Incompatible field of view An unsupported field of view. This example was captured with a 30° field of view, however the ARDA algorithm accepts images captured with a 40°-45° field of view.		Not Applicable
Single or two channel images An unsupported color. These example were captured with a single channel, however the ARDA algorithm accepts fundus images captured in 3-channel color or white light or RG composite UWF retinal images,		
Image with text An image with text present (in the top right of the image). Text may not be present anywhere on images, even in the black surrounding region. This is true regardless of whether or not the text is personally identifiable information (PII) or personal health information (PHI).		

5.2 Grading results from ARDA

After submitting an image to ARDA, the ARDA API runs a machine learning algorithm and returns results as described below. During the installation process, the ARDA API will be integrated into the electronic system of the clinical site, and the clinical site will be responsible for displaying the ARDA output in a format that is consistent with their clinical practice. Please check with your technical support staff for the exact format and location of display of the ARDA output.

5.2.1 Understand the grading system

The ARDA API provides an automated evaluation based on the International Clinical Diabetic Retinopathy (DR) and Diabetic Macular Edema (DME) Disease Severity Grading Scale. Specifically, the ARDA API provides results as indicated by **Figure 1 and 2** below.

Figure 1 Diagram that illustrates how ungradables are incorporated into ARDA diagnosis outputs for DR and DME

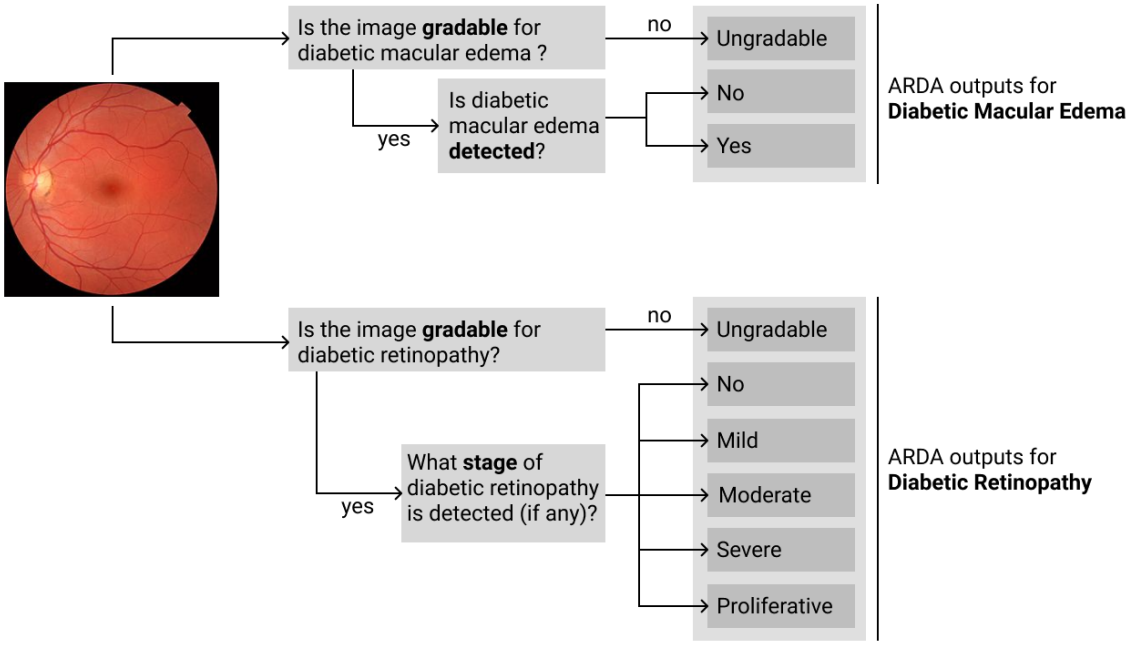


Figure 2 Diagram that illustrates how ungradables are incorporated into the ARDA diagnosis of UWF Retinal Images for DR and DME

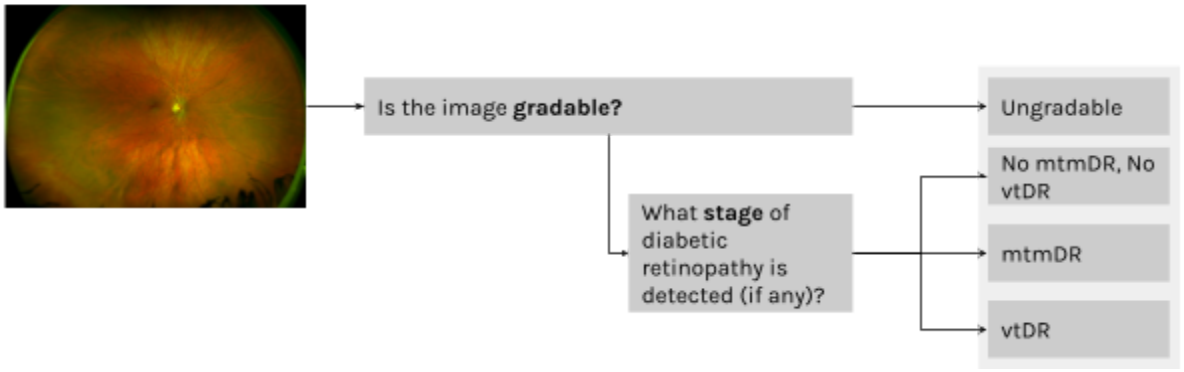


Image gradeability

The ARDA API analyzes each image to determine if it is gradable for DR and DME, which usually depends on the quality of the image (exposure, artifacts etc.). This gradability analysis is performed separately for DR and DME.

**Note: It is possible for an image to be gradable for DR and ungradable for DME, and vice versa.*

- A *Gradable* image is considered adequate for DR and/or DME grade analysis by ARDA. In this case, the ARDA API output of DR and/or DME grade is provided.
- An *Ungradable* image is considered inadequate for DR and/or DME grade analysis by ARDA. In this case, the ARDA API output is returned as "Ungradable" for DR and/or DME.

Ungradable Image troubleshooting

We recommend the following approaches to troubleshooting “Ungradable” results:

- If the algorithm returns “Ungradable” for DR or DME but also indicates referrable disease for a patient in at least one eye, refer the patient to an ophthalmologist instead of taking another image.
- If the algorithm returns "Ungradable" for DR or DME and does not indicate referrable disease, take another image and re-submit to ARDA for analysis. If the algorithm returns "Ungradable" a second time, refer the patient to see an eye care specialist for further evaluation.

Diabetic Retinopathy (DR) and Diabetic Macular Edema (DME)

The automated evaluation of DR and DME provided by ARDA is based on the International Clinical Diabetic Retinopathy (ICDR) severity scale. As per the Diabetic Retinopathy Preferred Practice Patterns (Updated 2017) from the American Academy

of Ophthalmology[1], this scale was formulated by a consensus of international experts to standardize and simplify DR and DME grading and to improve communication and coordination of care among physicians caring for patients with diabetes.

For DR gradable fundus images, the ARDA API will provide one of the following DR grades based on the 5-point ICDR Grading Scale:

- **No**, which means No apparent Diabetic Retinopathy
- **Mild**, which means Mild Nonproliferative Diabetic Retinopathy (NPDR)
- **Moderate**, which means Moderate NPDR
- **Severe**, which means Severe NPDR
- **Proliferative**, which means Proliferative Diabetic Retinopathy (PDR)

For DME gradable fundus images, the ARDA API will provide one of the following DME grades:

- **No DME**, which means "no hard exudates within 1 Disc Diameter of the fovea"
- **Yes DME**, which means "presence of hard exudates within 1 Disc Diameter of the fovea"

For UWF retinal images, the ARDA API will provide one of the following grades:

- Ungradable (image is considered inadequate for analysis by ARDA)
- No mtmDR (indicating presence of no or mild DR)
- Yes mtmDR but not vtDR (indicating presence of either moderate DR, severe DR, proliferative DR and/or DME)
- Yes vtDR (indicating presence of either severe DR, proliferative DR and/or DME that is vision-threatening)

5.2.2 How the grading algorithm works

The ARDA algorithm leverages machine learning to analyze a fundus or retinal image and discern high-level patterns and features.

The algorithms were developed using millions of images that were labeled by expert graders according to the 5-point ICDR disease severity scale and for presence of DME. The images were then fed to the algorithm, from which it "learned" to identify characteristics of DR and DME. This "training" allowed the algorithm to identify overarching, complex patterns associated with each DR severity level and the presence/absence of DME. Following the algorithm training and development, the

[1] American Academy of Ophthalmology Retina/Vitreous Panel. Preferred Practice Pattern® Guidelines. Diabetic Retinopathy. San Francisco, CA: American Academy of Ophthalmology; 2017.

performance of ARDA was validated in a dataset described in the Summary of ARDA Performance Evaluation section.

A fundus image submitted to ARDA receives a grade for DR and DME. If the image is not able to be analyzed by the algorithm, ARDA will identify the images as "ungradable." The specific severity grade for DR (from Mild to Proliferative) is determined using probabilities. The algorithm places thresholds on its probabilistic estimates for each severity level of DR and chooses the specific severity level if its probability is above the prespecified threshold.

An UWF retinal image submitted to ARDA receives a grade for mtmDR or vtDR. If the image is not able to be analyzed by the algorithm, ARDA will identify the image as "ungradable." The likelihood of a specific grade of DR is calculated as one or more continuous numbers, which are then combined and thresholded to result in two binary assessments (presence of mtmDR and vtDR). The algorithm chooses the level for which this combined assessment is above the pre-specified threshold. In case both mtmDR and vtDR meet the prespecified thresholds, the more severe level (vtDR) is provided as the final diagnosis.

5.3 Refer a patient to a specialist

The ARDA output does not include patient management or referral recommendations. It is the responsibility of the user to decide on the appropriate clinical management for each patient. Patients who are already under the care of an eye-care specialist should continue to follow the re-examination recommendations specified by their specialists unless the ARDA findings warrant an earlier re-examination.

The tables below summarizes the International Council of Ophthalmology (ICO) Guidelines for Diabetic Eye Care (Updated 2017)[2] used for referral or re-examination of DR/DME based on the severity findings.

Fundus Images

Findings	Referral or Re-examination Recommendation based on ICO Guidelines
No apparent DR, mild NPDR and no DME	Re-examination in 1-2 year
Moderate NPDR	Refer to eye-care specialist in 3-6 months
Severe NPDR	Refer to eye-care specialist within 3 months
PDR and/or DME	Refer to eye-care specialist within 1 month

UWF Retinal Images

Findings	Referral or Re-examination Recommendation based on ICO Guidelines
No mtmDR, no vtDR	Re-examination in 1-2 year
mtmDR	Refer to eye-care specialist in 3-6 months
vtDR	Refer to eye-care specialist within 1 month

[2] www.icoph.org/diabeticeyecare, Accessed 9/28/2018.

6.0 Summary of ARDA Performance Evaluation

An evaluation was completed to determine the performance of the ARDA algorithm for screening “more than mild” diabetic retinopathy (mtmDR).

- **mtmDR** is defined as presence of Moderate DR, or Severe DR, or Proliferative DR, and/or DME

The evaluation compared ARDA classifications to ground truth classifications on two sets of images, one set of fundus images and one set of UWF retinal images. Both sets of images were acquired from individuals with diabetes across a diversity of ethnicities. To establish the ground truth classifications, these images were graded by a panel of three expert human graders, with adjudication performed for cases where there was disagreement.

Image Set 1 consisted of 828 retrospectively collected fundus images acquired with five types of cameras: Crystalvue NFC-700, Canon CR-2, Topcon NW-400, Optovue iCam, CenterVue DRS. These 828 images were classified by **ground truth** as follows:

- 314 **No DR**, 130 **Mild DR**, 129 **Moderate DR**, 127 **Severe DR**, 128 **Proliferative DR**
- 616 **No DME**, 212 **Yes DME**
- 444 **mtmDR negative**, 384 **mtmDR positive**

Image Set 2 consisted of 438 retrospectively-collected UWF retinal images acquired with Optos P200T cameras. These 438 images were classified by **ground truth** as follows:

- 256 **mtmDR negative**, 182 **mtmDR positive**

The performance of the ARDA algorithm summarized below is based on the images that were considered gradable by both ground truth and by the ARDA software.

Summary of ARDA Performance		Set 1 (N=812)	Set 2 (N=420)
mtmDR Sensitivity	The proportion of images considered **positive** for mtmDR by ground truth that were correctly identified as such by ARDA, where positive for mtmDR is: ● ‘Moderate DR’ or ‘Severe DR’ or ‘Proliferative DR’ **and/or** ‘Yes DME’	90.3%	96.1%
mtmDR Specificity	The proportion of images considered **negative** for mtmDR by ground truth that were correctly identified as such by ARDA, where negative for mtmDR is: ● ‘No DR’ or ‘Mild DR’ **and** ‘No DME’	97.4%	93.4%

7.0 Troubleshoot ARDA

7.1 Technical problems with the API

The ARDA API is intended to be integrated into an existing healthcare IT system at your clinical site. If you are experiencing technical issues (e.g., slow connection, loss of service) with the API, please contact the IT administrators of your system.

ARDA provides feedback to technical systems describing its internal errors and data errors, and your IT team may be able to use this information to troubleshoot the problem. Please consult the ARDA Ingestion & Diagnosis Integration Guide (Doc # 100635, provided separately) for additional information regarding the error feedback provided by ARDA.

7.2 Other problems with the API

If you're having other problems with ARDA, you can contact the Verily Life Sciences support team at:

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- Elsewhere within the European Union: +44 20 76608851, or arda-success-eu@verily.com.
- Within India: 00 0800 0402 419, or arda-success-india@verily.com.

8.0 Regulatory Information

8.1 Name and address of manufacturer

Verily Life Sciences LLC
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South San Francisco, CA 94080

8.2 Authorized representative(s)

European Authorized Representative
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6827 AT Arnhem
The Netherlands

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Compass House, Vision Park, Histon,
Cambridge, United Kingdom, CB24 9BZ

India Importer
Morulaa HealthTech Pvt Ltd
Plot No. 38, First Floor, Rajeswari Street
Santhosh Nagar,
Kandanchavdi, Chennai - 600096, India

8.3 Regulatory statements

A paper copy of the IFU will be provided, if requested, at no additional cost to the user.

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Date: 06/17/2023
DOC #: 100462 Rev H

Contact support

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- Within the United Kingdom: 0800 026 3727 (Toll free number), or arda-success-eu@verily.com.
- Elsewhere within the European Union: +44 20 76608851, or arda-success-eu@verily.com.
- Within India: 00 0800 0402 419, or arda-success-india@verily.com.

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A paper copy of the IFU will be provided, if requested, at no additional cost to the user.

Intended for Export from the US.

Use with other ARDA Guides

The ARDA DICOM Conformance statement guide is intended to be used in conjunction with other ARDA Instructions for Use (IFUs). The table below explains the various ARDA deployment phases, and which IFUs should be used during each phase.

Deployment Phases	Applicable IFUs
*This document is applicable for **Phase 3***	
Phase 1 Familiarize yourself with ARDA's intended use and capabilities	ARDA User Guide (Doc # 100423), intended for **Healthcare Providers**
Phase 2 Fulfill the prerequisites to integrate with the ARDA APIs, including, but not limited to: obtaining access to Partner Issue Tracker, setting up GCP projects, requesting access to ARDA APIs	ARDA Google Cloud Platform Projects Setup Guide (Doc # 101304), intended for **Technical Support Staff**
Phase 3 Integrate your software with ARDA Ingestion and Diagnosis APIs	ARDA Ingestion & Diagnosis Integration Guide (Doc # 100635), intended for **Technical Support Staff** ARDA DICOM Conformance Statement (Doc # 100462), intended for **Technical Support Staff**
Phase 4 Perform installation qualification to ensure your integration with ARDA Ingestion and Diagnosis APIs was successful	ARDA Ingestion & Diagnosis Integration Guide (Doc # 100635), intended for **Technical Support Staff**
[Optional] Phase 5 Integrate your software with ARDA Medical Imaging Programs API for self-sufficient management of program creation This step may be done in parallel with **Step 3** and **Step 4**; those steps are not prerequisites for this step.	ARDA Medical Imaging Programs Integration Guide (Doc # 101187), intended for **Technical Support Staff**
Phase 6 Provision data silos (Programs) for clinical use. This might include creating new GCP Projects and provisioning new programs. Provisioning of programs will be performed by: • Interacting with ARDA Medical Imaging Programs API if **[Optional] Step 5** was performed, or • Requesting a Verily employee provision programs on your behalf by filing a ticket via Partner Issue Tracker if **[Optional] Step 5** was not performed	ARDA Google Cloud Platform Projects Setup Guide (Doc # 101304), intended for **Technical Support Staff**
Phase 7 Use ARDA in clinical environment	ARDA User Guide (Doc # 100423), intended for **Healthcare Providers**

1. Conformance Statement Overview

ARDA implements the STOW-RS service for storing DICOM SOP Instances into the ARDA systems. This conformance statement refers only to the DICOM conformance claim for receiving and storing SOP instances for Ophthalmic Photography images, and no other types of DICOM data.

Table 1-1 provides an overview of the network services supported by ARDA.

Table 1-1: Network Services

Network Service	User of Service (Client)	Provider of Service (Server)
STorage Over the Web (STOW)		
STOW-RS - Store Instances	No	Yes

2. Table of Contents

3. Introduction

3.1 Audience

This document is written for the people that need to understand how ARDA will integrate with their existing systems. This includes both those responsible for overall imaging network policy and architecture, as well as vendors / integrators who need to have a detailed understanding of the DICOM features of the product. This document contains some basic DICOM definitions so that any reader may understand how this product implements DICOM features. However, integrators are expected to fully understand all the DICOM terminology, how the tables in this document relate to the product's functionality, and how that functionality integrates with other devices that support compatible DICOM features.

3.2 Remarks

The scope of this DICOM Conformance Statement is to facilitate integration between ARDA and other DICOM products. The Conformance Statement should be read and understood in conjunction with the DICOM Standard. DICOM by itself does not guarantee interoperability. The Conformance Statement does, however, facilitate a first-level comparison for interoperability between different applications supporting compatible DICOM functionality. This Conformance Statement is not supposed to replace validation with other DICOM equipment to ensure proper exchange of intended information. In fact, the user should be aware of the following important issues:

- The comparison of different Conformance Statements is just the first step towards assessing interconnectivity and interoperability between the product and other DICOM conformant equipment.
- Test procedures should be defined and executed to validate the required level of interoperability with specific compatible DICOM equipment, as established by the healthcare facility.

3.3 Terms and Definitions

Application Entity (AE)
An end point of a DICOM information exchange, including the DICOM network or media interface software; i.e., the software that sends or receives DICOM information objects or messages. A single device may have multiple Application Entities.

Attribute
A unit of information in an object definition; a data element identified by a *tag*. The information may be a complex data structure (Sequence), itself composed of lower level data elements. Examples: Patient ID (0010,0020), Accession Number (0008,0050), Photometric Interpretation (0028,0004), Procedure Code Sequence (0008,1032).

Joint Photographic Experts Group (JPEG)
A set of standardized image compression techniques, available for use by DICOM applications.

Service/Object Pair Class (SOP Class)
The specification of the network or media transfer (service) of a particular type of data (object); the fundamental unit of DICOM interoperability specification. Examples: Ultrasound Image Storage Service, Basic Grayscale Print Management.

Service/Object Pair Instance (SOP Instance)
An information object; a specific occurrence of information exchanged in a *SOP Class*. Examples: a specific x-ray image.

Tag
A 32-bit identifier for a data element, represented as a pair of four digit hexadecimal numbers, the "group" and the "element". If the "group" number is odd, the tag is for a private (manufacturer-specific) data element. Examples: (0010,0020) [Patient ID], (07FE,0010) [Pixel Data], (0019,0210) [private data element]

Transfer Syntax
The encoding used for exchange of DICOM information objects and messages. Examples: *JPEG* compressed (images), little endian explicit value representation.

Unique Identifier (UID)
A globally unique "dotted decimal" string that identifies a specific object or a class of objects; an ISO-8824 Object Identifier[1]. Example: 1.2.840.10009.14.3.1. Usages include: Study Instance UID, SOP Class UID, SOP Instance UID.

Value Representation (VR)
The format type of an individual DICOM data element, such as text, an integer, a person's name, or a code. DICOM information objects can be transmitted with either explicit identification of the type of each data element (Explicit VR), or without explicit identification (Implicit VR); with Implicit VR, the receiving application must use a DICOM data dictionary to look up the format of each data element.

Value Multiplicity (VM)
The Value Multiplicity indicates the allowable number of values that a particular Tag may hold. Some VRs such as LO allow variable VM (e.g. 1-n), others such as LT require only a single value.

[1] http://dicom.nema.org/DICOM/2013/output/chtml/part05/chapter_9.html

3.4 Basics of DICOMweb Communication

DICOMweb is a set of RESTful APIs providing support for storing (STOW-RS), querying (QIDO-RS), and retrieving (WADO-RS) DICOM instances. Rather than using the “legacy” binary DIMSE protocols over TCP/IP, DICOMweb APIs use HTTPS, JSON and/or XML, as well as binary DICOM encodings. This allows for secure communication over the internet using standard encodings and protocols, without requiring specialized networking stacks that the DIMSE-based protocols require.

The RESTful DICOMweb APIs should not be confused with previous generation of Query-parameter-based APIs (WADO-URI) or SOAP-based DICOM protocols (WADO-WS, QIDO-WS). Their implementations and semantics are incompatible.

3.5 Additional Remarks about Software as a Service

ARDA is distributed as Software as a Service, via Google Cloud Platform. It is not an installable piece of software; installation and distribution is managed via Google Cloud Platform infrastructure and APIs.

See 4.2.1.2.2 URI Structure for details on the form and structure of accepted URIs for the ARDA DICOMweb services.

3.6 Abbreviations

AE: Application Entity
API: Application Programming Interface
ARDA: Automated Retinal Disease Assessment
CAD: Computer Aided Detection
DICOM: Digital Imaging and Communications in Medicine
DIMSE: DICOM Message Service Element
HTTP: Hypertext Transfer Protocol
HTTPS: Secure Hypertext Transfer Protocol
IOD: Information Object Definition
JPEG: Joint Photographic Experts Group
JSON: Javascript Object Notation
QIDO: Query based on ID for DICOM Objects
REST: Representational State Transfer
SAAS: Software as a Service
SCU: Service Class User
SCP: Service Class Provider
SOP: Service-Object Pair
STOW: Storage Over the Web
TCP/IP: Transfer Control Protocol / Internet Protocol

VR: Value Representation
WADO: Web Access to DICOM Objects
XML: Extensible Markup Language

3.7 References

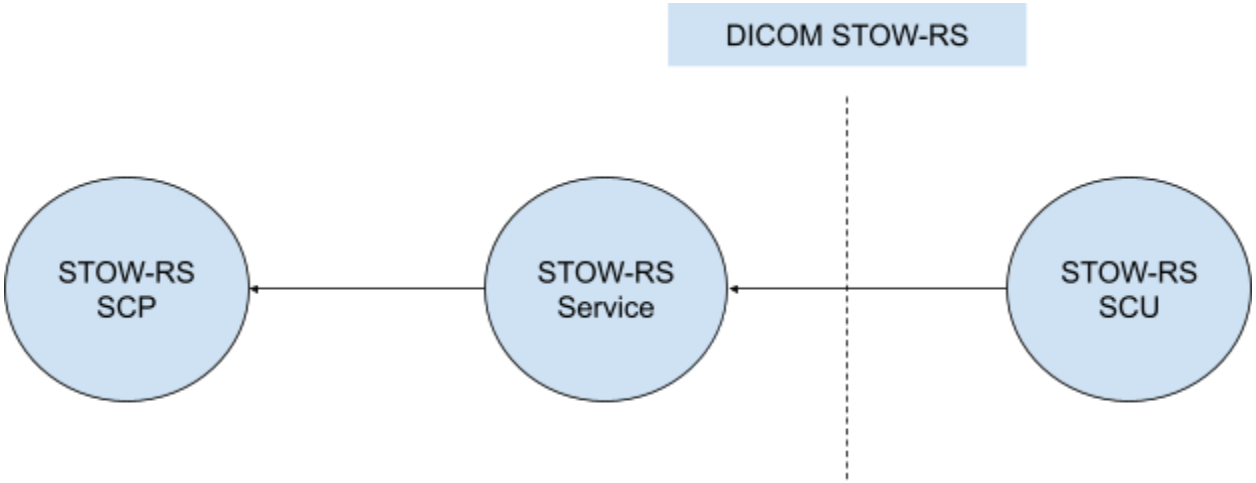
NEMA PS3 Digital Imaging and Communications in Medicine (DICOM) Standard, available free at http://medical.nema.org/

4. Networking

4.1 Implementation Model

4.1.1 Application Data Flow

Figure 4.1.1-1: STOW-RS Data Flow



The STOW-RS Service Application receives STOW requests from a remote AE. These requests are HTTPS POST requests. It is associated with the local real-world activity "Store Instances". It converts these requests into internal functions to store the given SOP Instances. It returns a summary HTTP status line, including a status code and an associated textual phrase, followed by an XML or JSON message indicating success, warning, or failure for each instance to the requesting remote AE.

4.1.2 Functional Definition of AEs

4.1.2.1 Functional Definition of STOW Service Application

The reception of a STOW-RS POST request will activate the STOW-RS Service. The storage request is based upon the accept headers in the STOW-RS POST request. The

response includes an HTTP/1.1 status line, including a status-code and its associated textual phrase, followed by an XML or JSON message indicating success, warning, or failure for each instance stored by the STOW-RS service.

4.2 AE Specifications

This AE complies with Section 6.6 “STOW-RS Request/Response” in DICOM PS3.18, specification for STOW-RS storage.

4.2.1 STOW-RS Specifications

4.2.1.1 STOW-RS Store Instance

Table 4.2-1: STOW-RS Store Instances Specification

Category	Restrictions
Request Transfer Syntaxes Supported (Media Type parameter)	Media Type must be one of: • application/dicom • application/dicom+xml • application/dicom+json Supported Transfer Syntaxes for binary DICOM data: • Explicit VR Little Endian - 1.2.840.10008.1.2 • Implicit VR Little Endian - 1.2.840.10008.1.2.1 • JPEG Baseline (Process 1) - 1.2.840.10008.1.2.4.50 • JPEG Lossless, Non-Hierarchical, First-Order Prediction (Process 14 [Selection Value 1]) - 1.2.840.10008.1.2.4.70 Supported Transfer Syntaxes for XML / JSON metadata: • Explicit VR Little Endian - 1.2.840.10008.1.2 • Implicit VR Little Endian - 1.2.840.10008.1.2.1 Supported Image Formats for uploads using DICOM-JSON or DICOM-XML: • image/jpeg • image/png
Response Media Types Supported (Accept header)	Restricted to application/dicom+json or application/dicom+xml. If neither are explicitly specified in the Accept header, application/dicom+xml will be returned by default, provided there is a wildcard (*) entry specified.
SOP Class Restrictions	Supported SOP Classes: • Ophthalmic Photography 8-Bit Image Storage - 1.2.840.10008.5.1.4.1.1.77.1.5.1

	• Wide Field Ophthalmic Photography Stereographic Projection Image Storage - 1.2.840.10008.5.1.4.1.1.77.1.5.5
Size restriction	No restriction on file size.

For more details, see **8.2 Acceptance Requirements for Ophthalmic Photography Instances**.

4.2.1.2 Connection Policies

4.2.1.2.1 General

The ARDA STOW-RS service is a Google Cloud API, all connections must be made in the context of a Google Cloud Project. The Google Cloud Project must have the Medical Imaging API enabled.

All requests must contain an OAuth2 Bearer Token supplied via the **Authorization** header; this OAuth2 Bearer Token shall contain an API Key for a Google Cloud Project, with the OAuth2 scope URL `https://www.googleapis.com/auth/lifescience.dicomweb`.

Any connections made without a Bearer Token with the proper scope and API Key will be rejected with a 401 - Unauthorized response.

4.2.1.2.2 URI Structure

All DICOMweb connections to ARDA must be made using base URIs of the form `https://medicalimaging.googleapis.com/v1/dicom/{program-id}/studies`. The {program-id} is a unique identifier for a particular Program, which is a deployment of the ARDA system. Please refer to ARDA's Instructions For Use for how to create and configure a Program for use with ARDA and DICOMweb.

4.2.1.2.3 Number of Connections

The ARDA STOW-RS service does not limit the number of simultaneous connections per se; instead each Google Cloud Project may make a certain number of requests per 100-second period. By default the limit is set at 500 requests per 100 seconds, or about 5 requests per second. Please contact Verily Life Sciences LLC support [VUS # and ARDA-success@verily.com] to request increased quota.

4.2.1.2.4 Asynchronous Nature

ARDA does not support asynchronous responses.

4.2.1.2.5 SOP Specific Conformance for SOP Classes

The ARDA response message header contains status codes indicating success, warning, or failure as shown in the "HTTP/1.1 Standard Response Codes" below. No additional status

codes are used.

Table 4.2.1.2.5-1. HTTP/1.1 Standard Response Codes

HTTP/1.1 Standard Response Codes			
Status	**Code**	**Description**	**Troubleshooting**
Failure	400 - Bad Request	This indicates that the STOW-RS Service was unable to store any instances due to bad syntax.	Review response body for explanation of specific issues and fix if possible.
	401 - Unauthorized	This indicates that the STOW-RS Service refused to create or append any instances because the client is not authenticated.	Authentication credentials are either not present or invalid. Ensure that proper credentials are provided in the request per Section 4.2.1.2.1.
	403 - Forbidden	This indicates that the STOW-RS Service understood the request, but is refusing to fulfill it (e.g., an authenticated user with insufficient privileges).	The authentication credentials provided in the request are valid, but not associated with the requested resource. Ensure that the requested resource is owned by the requesting account.
	409 - Conflict	This indicates that the STOW-RS Service request was formed correctly but the service was unable to store any instances due to a conflict in the request (e.g., unsupported SOP Class or Study Instance UID mismatch). This may also be used to indicate that a STOW-RS Service was unable to store any instances for a mixture of reasons. Additional information regarding instance errors can be found in the response message body.	Review response body for explanation of specific issues. DICOM Status Codes should help indicate which individual SOP Instances were associated with the conflict.
Warning	202 - Accepted	This indicates that the STOW-RS Service stored	Additional information regarding this warning can be found in the

		some of the instances but warnings or failures exist for others.	response message body.
Success	200 - OK	This indicates that the STOW-RS Service successfully stored all the instances.	N/A

The status codes above are returned in ARDA STOW-RS response headers. The ARDA STOW-RS response message body (PS3.18 XML Store Instances Response Module) may contain DICOM status codes for individual SOP Instances indicating success, warning, or failure. The table below lists values that may be used for the Failure Reason (0008,1197). In the event that multiple codes may apply, the single most appropriate code shall be used.

DICOM Failure Reason Status Code	Description
0110 - Processing failure	The STOW-RS Service did not store the instance because of a general failure in processing the operation. There may be a FailureReason private tag included with additional details; see 8.1 Data Dictionary of Private Attributes.
Cxxx - Error: Cannot understand	The STOW-RS Service did not store the instance because it cannot understand certain Data Elements.
C122 - Referenced Transfer Syntax not supported	The STOW-RS Service did not store the instance because it does not support the Transfer Syntax for the instance.

4.3 Network Interfaces

4.3.1 Physical Network Interface

ARDA uses Google Cloud Platform network interfaces; as ARDA is a managed API, the details are not relevant to this conformance statement.

4.3.2 Additional Protocols

ARDA supports both HTTP 1.1 and HTTP 2 connections.

4.3.3 IPv4 and IPv6 Support

This product supports both IPv4 and IPv6 connections.

4.4 Configuration

4.4.1 STOW-RS Interface

ARDA is configured to respond only to TLS protected traffic.

5 Media Interchange

Not Applicable.

6 Support of Character Sets

ARDA supports Unicode UTF-8 for all RS transactions.

ARDA does not convert character sets when storing PS3.10 binary Instances. The original DICOM encoded character sets are preserved.

7 Security

ARDA only accepts connections over HTTPS; unencrypted plain-HTTP requests are not accepted.

ARDA only accepts connections with proper credentials, in the form of an OAuth2 Bearer Token. See **Section 4.2.1.2.1 - General** for details about the types of credentials which are accepted.

8 Annexes

8.1 Data Dictionary of Private Attributes

The Private Attributes which may be present in a STOW-RS response are listed in the table below. ARDA reserves blocks of private attributes in group 0009 with the **Private Creator** value of `GOOGLE`.

Tag	Attribute Name	VR	VM
(0009,00xx)	Private Creator	LO	1
(0009,0097)	Failure Detail	LT	1

Failure Detail
This tag is conceptually an extension of **(0008,1197) Failure Reason**. It may contain, as

free-form text, an explanation of why a particular Instance could not be processed.

8.2 Acceptance Requirements for Ophthalmic Photography Instances

ARDA is designed to process Ophthalmic Photography images and associated DICOM tags. Refer to the table below for a list of tags that ARDA handles. Note that ARDA requires limited de-identification of DICOM metadata to ensure patient privacy and allow for long-term use of images for product improvement.

For information about the data type and format of any tag refer to the tag's VR in Table 6.2-1 in the DICOM standard.

DICOM Tag	DICOM Attribute	ARDA Requirements
(0008,0018)	SOP Instance UID **Required**	A globally unique "dotted decimal" string that identifies a specific DICOM object instance; an ISO-8824 Object Identifier. Example: 1.2.840.10009.14.3.1 Clients may specify a SOP Instance UID when making requests to ARDA for diagnosis of image data. The SOP Instance UID signifies that diagnosis is requested on the single image associated with the given SOP Instance UID.
(0020,000D)	Study Instance UID **Required**	A globally unique "dotted decimal" string that identifies a specific study; an ISO-8824 Object Identifier. Example: 1.2.840.10009.14.3.1 At most two images may be ingested for use with ARDA that are associated with the same Study Instance UID. Clients may specify a Study Instance UID when making requests to ARDA for diagnosis of image data. The Study Instance UID signifies that diagnosis is requested on all images associated with the given Study Instance UID.
(0008,0060)	Modality **Required**	Must be "OP" (the DICOM abbreviation for Ophthalmic Photography).
(0008,0070)	Manufacturer **Required**	Per DICOM specification.
(0008,0080)	Institution Name **Optional**	Per DICOM specification.
(0008,1090)	Manufacturer Model Name **Optional**	Per DICOM specification.
(0008,0020)	Study Date **Required**	Per DICOM specification.
(0008,0030)	Study Time	Per DICOM specification.

	Required	
(0008,0008)	Image Type **Required**	This multi-valued tag must conform to the format: *"[ORIGINAL or DERIVED]\[PRIMARY or SECONDARY]\\[COLOR* or blank]\[*PRIMARY* or *OPTOMAP* or blank]" In other words: ● Value 1 must be *ORIGINAL* or *DERIVED*[1] ● Value 2 must be *PRIMARY* or *SECONDARY*[2] ● Value 3 must be blank ● Value 4 must be blank or *COLOR* ● Value 5 must be blank or *PRIMARY* or *OPTOMAP*[3] Additional information can be specified after Value 5, but will be ignored by ARDA. For instance, this tag would be accepted if it were specified as "ORIGINAL\PRIMARY\\\PRIMARY\thiswillbeignored" [1] *ORIGINAL* signifies an image with pixel values based on original or source data; *DERIVED* signifies an image with pixel values derived in some manner from the pixel value of one or more other images [2] *PRIMARY* indicates an image created as a direct result of the Patient examination; *SECONDARY* indicates an image created after the initial Patient examination [3] *PRIMARY* is applicable to 45-degree image data and indicates a field of view within the retina that contains both the macula and optic disc and is centered between them; *OPTOMAP* is applicable to UWF image data
(0010,0010)	Patient Name **Do not include**	Must be either absent or empty (""").
(0010,0020)	Patient ID **Required**	Unique & anonymized identifier. This could be a combination of numbers, letters, punctuation marks, etc. **ARDA clients are responsible for anonymization of patient identifiers prior to transmission.** That is, patient IDs should not contain any identifiable information such as name, address, date of birth, social security number, or other information considered personally identifiable or that could be used to identify an individual. Consult your company's policies on proper anonymization techniques.
(0010,0030)	Patient Birth Date **Optional**	If present, must be of the form YYYY0101, where YYYY is the year of birth. Images from a patient who is less than 18 years old will be rejected.
(0010,0040)	Patient Sex **Optional**	If present, accepted values are *M* (male), *F* (female), and *O* (other). This field should indicate the patient's sex at

		birth.
(0012,0083)	Consent for Clinical Trial Use Sequence **Required**	This is a sequence DICOM tag that must include the following 3 nested tags: 1. *Clinical Trial Protocol ID* 2. *Consent for Distribution Flag* 3. *Distribution Type*
(0012,0020)	>Clinical Trial Protocol ID **Required**	Accepted values are: ● *Arda Diagnosis* ● *Arda Improvement*
(0012,0084)	>Distribution Type **Required**	Accepted values are: ● *NAMED_PROTOCOL* ● *RESTRICTED_REUSE* ● *PUBLIC_RELEASE*
(0012,0085)	>Consent for Distribution Flag **Required**	Must be *YES*.
(0020,0060)	Laterality **Optional**	If present, must be identical to tag *Image Laterality*.
(0020,0062)	Image Laterality **Required**	Accepted values are *L* (left eye) and *R* (right eye).

HTTP Request	ARDA Requirements
JPEG or **PNG** image	Depending on the device, each JPEG or PNG image specified must adhere to specific requirements. ● For **45 image data -** This JPEG or PNG image must be a primary field of view, where the macula and optic nerve are equally distant from the center of the image. Images must be taken using either 3-channel color (also known as true/natural color images) or white light. No text may be present anywhere (even within the black surrounding mask region) on an image. ● For **UWF image data -** This JPEG or PNG image must be centered at the macula. Images must be taken using RG color composite (also known Optomap color). No text may be present anywhere (even within the black surrounding mask region) on an image.

DICOM Tag	DICOM Attribute	ARDA Requirements
(0008,0016)	SOP Class UID **Required**	● For **45 image data -** Must be *1.2.840.10008.5.1.4.1.1.77.1.5.1* (the SOP Class UID for Ophthalmic Photography 8 Bit Image Storage instances) ● For **UWF image data -** Must be *1.2.840.10008.5.1.4.1.1.77.1.5.5* (the SOP Class UID for Wide Field Ophthalmic Photography Stereographic Projection Image Storage instances)
(0022,000C)	Horizontal Field of View **Required**	● For **45 image data -** Must be 45 ● For **UWF image data -** Must be 200
(0028,0010)	Rows **Required**	● For **45 image data -** Must be at least 1024 ● For **UWF image data -** Must be 4000

(0028,0011)	Columns **Required**	• For **45 image data -** Must be at least 1024 • For **UWF image data -** Must be 4000