OPERATING MANUAL
RAYVOLVE

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This document covers Rayvolve Version 2, and all related minor releases

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FOR US ONLY

INSTRUCTIONS FOR USE

I. General

a. Description

Rayvolve is a computer-assisted detection and diagnosis (CAD) software device to assist radiologists and emergency physicians in detecting fractures during the review of radiographs of the musculoskeletal system.

b. Destination, intended users and intended patient population

Rayvolve is designed to help MSK and non-MSK radiologists and emergency physicians.
Rayvolve is indicated for adults only (≥ 22 years old).

c. Indications for use

Rayvolve is a computer-assisted detection and diagnosis (CAD) software device to assist radiologists and emergency physicians in detecting fractures during the review of radiographs of the musculoskeletal system. Rayvolve is indicated for adults only (≥ 22 years old). Rayvolve is indicated for radiographs of the following industry-standard radiographic views and study types.

Study Type (Anatomic Area of Interest)/ Radiographic views supported:

- Ankle / Frontal, Lateral, Oblique
- Clavicle / Frontal
- Elbow / Frontal, Lateral
- Forearm / Frontal, Lateral
- Hip / Frontal, Lateral
- Humerus / Frontal, Lateral
- Knee / Frontal, Lateral
- Pelvis / Frontal
- Shoulder / Frontal, Lateral, Axillary
- Tibia/fibula / Frontal, Lateral
- Wrist / Frontal, Lateral, Oblique
- Hand / Frontal, Lateral
- Foot / Frontal, Lateral

“Frontal” is considered inclusive of both posteroanterior (PA) andanteroposterior (AP) views. Definitions of anatomic area of interest and radiographic views are consistent with the American College of Radiology (ACR) standards and guidelines.

d. Undesirable side effects

No adverse side effects related to the use of Rayvolve have been reported.

e. Warnings

- Rayvolve is an adjunct tool and does not replace the role of the users : they must not use the output of Rayvolve as primary interpretation.
- The users may use Rayvolve only for the intended anatomical regions: Ankle, clavicle, elbow, forearm, hip, humerus, knee, pelvis, shoulder, tibia/fibula, wrist, hand, foot: the users may rely on their own diagnostic if ever Rayvolve detects fractures from anatomical areas outside the indication for use.
- The same bounding box can contain several adjacent fractures: the users shall proceed to a concurrent read with the original X-ray.
- It is possible that a bounding box hides a part of an adjacent fracture the users shall proceed to a concurrent read with the original X-ray.
- Rayvolve is not designed and tested to be used with pediatric patients under 22 years old
- Rayvolve is not intended to detect fractures in other modalities that X-rays
- Rayvolve is not intended to detect fractures from anatomical areas of interest outside the indication for use: user should review original images for all other suspected pathologies and other anatomical regions
- Poor image quality can affect Rayvolve's detection of fracture: the users shall proceed to a concurrent read with the original X-ray.
- In the event of a significant change in Rayvolve's performance, please contact AZmed.
- Rayvolve is a diagnostic aid, only the users' diagnosis remain valid for the patient.
- Any serious incident occurring in connection with the device should be notified to AZmed and to the competent authority in which the user is established.

f. Contraindication and precautions

- Do not use Rayvolve to detect foreign matters
- If Rayvolve encounters an image or an exam outside of the anatomic areas of the indication for use, it will not be processed by Rayvolve and no Secondary Capture image will be generated by Rayvolve.
- If Rayvolve encounters an exam inside of the anatomic areas of the indication for use, but the exam contains a part or an entire fracture outside of the anatomic areas in the indications for use (for instance a rib fracture present in a shoulder exam), Rayvolve will process the image. If Rayvolve processes the exam the user should not consider the analysis of Rayvolve regarding the part of the image outside of the anatomic areas in the indication for use.

g. Cybersecurity Recommendations

AZmed addressed cybersecurity during the design and development of Rayvolve. Cybersecurity threats are continuously monitored.

To ensure a safe connexion of Rayvolve to your local network and PACS, AZmed recommends the following cybersecurity specifications:

- A VPN for the remote maintenance,
- A firewall to control and limit to only needed incoming and outgoing network traffic,

- A PACS with a TLS connexion ensures secure exchanges of DICOM file.

If you have any doubt that Rayvolve has been altered, please contact AZmed contact immediately the technical support of AZmed on support@azmed.co.

h. Notes

No residual risks were identified for Rayvolve.

II. Mode of operation

Once Rayvolve has been installed by AZmed's technical teams, Rayvolve will interact directly with your medical image server (PACS). No action is needed to get Rayvolve working for your analysis, Revolve will work automatically whenever you want to analyze an image.

When connected to the PACS Server:

1. Rayvolve analyses anonymized X-rays.
2. Rayvolve generates in the same series of images a Secondary Capture image containing predictions of the presence or absence of anomalies, in the same study of images without altering the original image
    - Any prediction is displayed on a Secondary Capture image identifiable by the AZmed logo.
    - When a fracture is detected by Rayvolve, it is framed by abright white bounding box on the Secondary Capture image.
    - When Rayvolve detects no fracture, the phrase "No Anomaly detected" is displayed at the top of the Secondary Capture image.
3. Revolve automatically generated a secondary report of Rayvolve analysis in the same exam with the Secondary Capture image.

Any inquiries about our display should be directed to support@azmed.co.

III. Installation and maintenance

Installation and maintenance are carried out only by AZmed. During this installation, AZmed will provide the specifications of your system. Please check with an AZmed technician that Rayvolve is working properly after installation or maintenance.

AZmed is not responsible if you install or carry out the maintenance of Rayvolve yourself.

IV. Performances claimed

Based on standalone performance testing and on the clinical investigation, we claim that radiologist and emergency physicians:

- improve their performances in detecting and localizing anomalies on standard radiographs when supported by Rayvolve’s prediction
- reduce their x-rays analysis time

V. Storage conditions and disposal of the case

For optimal use, the case should be placed in a room at ambient temperature and kept more than 20 cm from an operator.
The case and the computer kit lifetime is up to 5 years after installation. Rayvolve software runs continuously until it is disposed of. Under no circumstances should you dispose of Rayvolve yourself.
AZmed is responsible to change the hardware before the expiry date. Please contact AZmed for disposal.

VI. Software Update

The software runs continuously and may be subject to regular version updates of which you will be informed as soon as possible. Updates of version are realized by AZmed only. An email will be sent to the user when an update is available.

VII. Software Uninstallation

You cannot uninstall Rayvolve on your own. Contact AZmed's technician team to uninstall Rayvolve.

VIII. Symbols signification

The table below describes all symbols displayed on the label of the product:

Symbol	Name	Description
	Manufacturer	Indicates the medical device manufacturer. It is accompanied by the manufacturer's name & address
	Date of manufacture	Indicates when the medical device was manufactured. It is accompanied by the product version release date (date of manufacture).
	Catalogue number	Indicates the manufacturer's catalogue number so that the medical device can be identified.
	UDI	Indicates the Unique Device Identifier of the device.
	Consult electronic instructions for use	Indicates that the Instructions for Use for the device are in electronic form and should be consulted.
	Medical device	Indicates that the Rayvolve is a medical device.
	Swiss representative	Indicates the swiss authorized representative.
	Caution	Indicates that there are specific warnings or precautions associated with the device which are not found on the label. These precautions/warnings are described in the Instructions for Use.
	CE mark	Indicates that the medical device has been awarded the CE mark by the notified body BSI (2797).

SN	Serial number	Indicates the manufacturer’s serial number so that a specific medical device can be identified.
	Keep dry	Indicates that the medical device needs to be protected from moisture.
	Keep away from sunlight	Indicates that the medical device needs protection from light sources.

TECHNICAL DATA SHEET

I. Minimum configuration

Rayvolve medical device is designed to work in combination with your PACS Server. It interacts directly with DICOM images to generate a Secondary Capture on which the prediction will be displayed.

To do this, Rayvolve requires a direct connection to your PACS. So, Rayvolve should be able to connect to your PACS (and your local network if needed) and should be added as a modality to your PACS with Rayvolve AET, IP and PORT (provided by AZmed).

II. Technical characteristics of the software

Rayvolve analyses standard radiographs and displays the prediction according to the following characteristics:

- Any prediction is displayed on a Secondary Capture (drated images are identifiable by the AZmed Logo displayed in the lower right corner of the image.
- When an anomaly is detected by Rayvolve, it is framed by a bright white bounding box on the generated image.
- When no anomaly is detected by Rayvolve, the phrase "No anomaly detected" is displayed at the top of the generated image.

Rayvolve operates continuously as soon as it is connected to the PACS.

III. Minimum characteristics and configuration of the IT Network

As Rayvolve does not require a specific connection to the IT network to function, no minimum requirement at the network level are necessary.

Rayvolve only needs to be connected to the PACS server.

If required, Rayvolve can be connected to the PACS server through a Virtual Private network (VPN), which is a communication channel that automatically encrypts the data exchanges and ensures confidentiality of the information exchanged.

IV. Access to the electronic instruction for use (eIFU)

In order to access the instructions for use in electronic format, you must have software that allows you to read documents in PDF format.

Access to the online instructions for use is provided through the following link: https://azmed.co/e-ifu.pdf.
To access this link, you must have internet access and a web browser.

In case of any problem with your browser, please contact AZmed immediately, which will provide you with the IFU in PDF format by email.

In case of a problem with your internet access, please contact AZmed immediately, who will send you the IFU at no extra cost within a reasonable time and at the latest within seven calendar days following the reception of your request.

V. System requirements for maintenance

For maintenance purposes, Rayvolve needs to be connected to the PACS server.

VI. Action of the software in case of failure

If Rayvolve does not work as intended of Rayvolve, please contact the technical support of AZmed on support@azmed.co.

VII. Dangerous situations in the event of failure of the IT network or the PACS

The management of these risks at the level of the IT network and PACS is the responsibility of the medical center. Any modification of the IT network or the PACS server is likely to bring unidentified risks that must be controlled and then reported to AZmed. In particular when the following situations occur:

- In case of failure of the IT network that could lead to a malfunction of the PACS server
- Changes in the configuration of the IT network;
- The addition of a similar device (compared to Rayvolve) to the PACS.

VIII. Rayvolve compatibility with the image acquisition systems and imagines protocols

Rayvolve is compatible with all the digital X-ray imaging hardware (modality CR, RF, DX) and all the X-ray protocols which include the anatomical regions analyzed by Rayvolve.

IX. Flow matrix

A matrix of outgoing and incoming flows in Excel format or according to the institution's model can be sent on request. This flow matrix specifies the flows necessary for the proper functioning of Rayvolve and also the temporary access to the Internet in order to install the various software and libraries necessary before going into production.

RAYVOLVE CLINICAL STUDY SUMMARY

Rayvolve performance was validated through two studies:

- A standalone performance study in order to demonstrate that Rayvolve has equivalent performance throughout its indication for use's anatomical regions and confounders.
- A Multiple Reader Multiple Case study in order to demonstrate that Rayvolve improves the clinicians' performance in detecting and localizing fractures on radiographs of the musculoskeletal system.

THE STANDALONE PERFORMANCE STUDY

Data set/tested subgroups:

For both standalone and MRMC studies, the subgroups have been determined based on the data set composed with the following inclusion criteria:

- De-identified radiographs
- Frontal, LAT, Oblique and Axillary views
- Adult patient, minimum of 22 years of age

Regarding the performance standalone study:

Here are the different subgroups/confounders evaluated:

- Gender
- Age
- Anatomic region
- Machine acquisition
- Machine view
- Weight-bearing radiographs
- Complex and uncommon radiographs

Based on statistical tools, we estimated a minimum of 26 radiographs per subgroup (with at least 13 positive radiographs and 13 negative radiographs) per indication for use subgroups. The performance assessment has been made on 2626 radiographs for all the study types (anatomic areas of interest) and views in the indication for Use.

Data collection and storage:

Data is retrieved and stored on a Health Data Hosting approved hosting server (HIPAA-compliant, located within the US). In compliance with the AZmed cybersecurity process, radiographs that are collected from the clinical partner are pseudonymized.

Confounders:

Confounders are considered as factors in a multivariate logistic model: device, age group, radiograph views, anatomic area and type of fracture.

STANDALONE PERFORMANCE STUDY

The results of the standalone testing demonstrated that Rayvolve detects fractures of the musculoskeletal system radiographs with high AUC and sensitivity and specificity across the following subgroups:

Subgroups	Data set distribution (%)	AUC (Bootstrapped CI)	Sensitivity (95% Wilson's CI)	Specificity (95% Wilson's CI)
All	100	0.98607 (0.98104; 0.99058)	0.98763 (0.97559, 0.99421)	0.88558 (0.87119, 0.89882)
PER GENDER				
Male	49.7	0.98822 (0.98186; 0.99409)	0.99067 (0.97023, 0.99650)	0.88724 (0.86665, 0.90557)
Woman	50.3	0.98395 (0.97589; 0.99101)	0.98462 (0.96094, 0.99274)	0.88394 (0.86284, 0.90210)
PER VIEWS				
Frontal	48.7	0.97872 (0.96845; 0.98805)	0.97453 (0.95018, 0.98805)	0.88554 (0.86508, 0.90458)
Lateral	39.3	0.99218 (0.98903; 0.99477)	1.0 (0.98307, 1)	0.88393 (0.86006, 0.90422)
Oblique	10.2	0.9958 (0.98979; 0.99977)	1.0 (0.94499, 1)	0.89076 (0.84061, 0.92697)
Axillary	1.8	0.99675 (0.98734; 1.0)	1.0 (0.77190, 1)	0.8961 (0.76427, 0.96860)

PER AGE

Subgroups	Data set distribution (%)	AUC (Bootstrapped CI)	Sensitivity (95% Wilson's CI)	Specificity (95% Wilson's CI)
22-60	53.4	0.99049 (0.98359; 0.99598)	0.99095 (0.97102, 0.99659)	0.88194 (0.86177, 0.89986)
> 60	46.6	0.98102 (0.97487; 0.98941)	0.98415 (0.96472, 0.99457)	0.8899 (0.86829, 0.90843)

PER MACHINE PROVIDER

Subgroups	Data set distribution (%)	AUC (Bootstrapped CI)	Sensitivity (95% Wilson's CI)	Specificity (95% Wilson's CI)
GEHC Discovery XR 656	47	0.98482 (0.97920; 0.99264)	0.98582 (0.96410, 0.99447)	0.87032 (0.85586, 0.89301)
Philips DigitalDiagnost	32	0.98635 (0.97657; 0.99345)	0.98218 (0.95355, 0.99957)	0.88583 (0.86686, 0.91909)
Carestream Health DRX-1	21	0.98842 (0.97754; 0.99689)	1.0 (0.94420, 1)	0.92029 (0.87638, 0.95582)

PER ANATOMICAL AREA

Subgroups	Data set distribution (%)	AUC (Bootstrapped CI)	Sensitivity (95% Wilson's CI)	Specificity (95% Wilson's CI)
Ankle	8.8	0.99137 (0.98374; 0.99727)	1 (0.93472,1)	0.86224 (0.80617, 0.90716)
Clavicle	6.9	0.97806 (0.94626; 0.99761)	0.97766 (0.87404, 0.99884)	0.89659 (0.82738, 0.93589)
Elbow	7.3	0.9964 (0.99059; 1.0)	1 (0.90109, 1)	0.90123 (0.84617, 0.94716)
Forearm	5.9	0.9953 (0.98909; 0.99937)	1 (0.90358, 1)	0.87786 (0.80551, 0.92342)
Humerus	6.8	0.9955 (0.98960; 0.99943)	1 (0.90594, 1)	0.86111 (0.79520, 0.90826)
Hip	7.5	0.95821 (0.93239; 0.98014)	0.95652 (0.87246, 0.98959)	0.88108 (0.82026, 0.92550)
Knee	9.1	0.97742 (0.95084; 0.99592)	0.97561 (0.90695, 0.99899)	0.8756 (0.82312, 0.91708)
Pelvis	5.7	0.97676 (0.95241; 0.99638)	0.97505 (0.91057, 0.99903)	0.9025 (0.84446, 0.94161)
Shoulder	5.7	0.97814 (0.94147; 0.99958)	0.96429 (0.88405, 0.99875)	0.90135 (0.83828, 0.94271)
Tibia/Fibula	8.8	0.98285 (0.95925; 0.9978)	0.97778 (0.88433, 0.99886)	0.88942 (0.83443, 0.92537)
Wrist	8.5	0.99567 (0.99126; 0.99897)	1 (0.92590, 1)	0.87624 (0.81898, 0.91647)
Hand	9.6	0.99552 (0.99074; 0.99898)	1 (0.94935, 1)	0.89444 (0.84103, 0.93138)
Foot	9.4	0.99162 (0.98238; 0.99823)	1 (0.93581, 1)	0.90722 (0.85669, 0.93988)

PER OTHER SUBGROUPS

Subgroups	Data set distribution (%)	AUC (Bootstrapped CI)	Sensitivity (95% Wilson's CI)	Specificity (95% Wilson's CI)
Complex & uncommon	21	0.96102 (0.95223; 0.99615)	0.96124 (0.94623, 0.97801)	0.83596 (0.82996, 0.85896)
Non – "complex & uncommon"	79	0.99607 (0.98862; 0.99701)	0.99506 (0.98386, 0.99877)	0.89837 (0.88182, 0.90910)
Weight-bearing	49	0.98059 (0.96162; 0.99458)	0.98174 (0.90835, 0.99764)	0.88580 (0.83074, 0.92533)
Non-weight bearing	51	0.99143 (0.97916; 0.99912)	0.99296 (0.91280, 0.99972)	0.88678 (0.82527, 0.92888)

SUMMARY

1. Rayvolve detects fractures of the musculoskeletal system radiographs with high sensitivity, high specificity and high Area Under The Curve (AUC) of the Receiver Operating Characteristic (ROC).

2. Rayvolve performs with high accuracy across study types and potential confounders (anatomic areas of interest, views, patient age and sex, image acquisition, and types of fractures)

3. Rayvolve presents high accuracy across the different types of fractures (complex & uncommon, Non-"complex & uncommon", weight-bearing, non weight-bearing)

THE MRMC STUDY

A total of 24 readers (8 Emergency doctors, 8 "non-MSK" radiologists, 8 MSK radiologists) evaluated 186 cases under aided and unaided conditions. The cases are randomly sampled from the validation dataset
used for the standalone performance study. The number of readers and cases analyzed by the readers were determined following the Rayvolve predicate.

The readers training

The readers involved in the study are informed with the protocol of the study. They have been adequately instructed and trained in the proper use of device for the truthing and reading process.

Dataset:
Here are the different subgroups/confounders evaluated:
- Gender
- Age
- Machine acquisition

THE MRMC STUDY RESULTS

PER ANATOMICAL AREA

Subgroups	Data set distribution (%)	AUC (Bootstrapped CI) improvement	Sensitivity improvement	Specificity improvement	Time improvement
Ankle	9,1	0.02386 (0.01705; 0.04134)	0.05208	0.00301	3.49s (11%)
Clavicle	5,4	0.03870 (0.02809; 0.05473)	0.07292	0.00000	6.20s (31%)
Elbow	8,1	0.04560 (0.02653; 0.05344)	0.06944	0.00694	3.27s (16%)
Forearm	5,4	0.05028 (0.03194; 0.05849)	0.06250	0.00694	17.27s (46%)
Humerus	7	0.05768 (0.04275; 0.08504)	0.12500	0.00000	11.46s (30%
Hip	7,5	0.05140 (0.03881; 0.07286)	0.10833	0.00463	4.31s (14%)
Knee	9,7	0.06203 (0.04977; 0.07676)	0.10714	0.01106	3.04s (17%)
Pelvis	4,8	0.05103 (0.03961; 0.06622)	0.13889	0.00624	5.81s (21%)
Shoulder	7	0.01241 (0.00927; 0.02010)	0.02183	0.00926	5.69s (29%)
Tibia/Fibula	9,1	0.02358 (0.00861; 0.03039)	0.05952	0.00000	5.49s (30%)
Wrist	10,2	0.06480 (0.04608; 0.07398)	0.10978	0.00728	6.42s (29%)
Hand	9,1	0.04465 (0.03631; 0.05819)	0.08343	0.00000	13.99s (46%)
Foot	7,5	0.08656 (0.06288; 0.10960)	0.13333	0.00423	8.98s (29%)

Subgroups	Data set distribution (%)	AUC (Bootstrapped CI) improvement	Sensitivity improvement	Specificity improvement	Time improvement
PER AGE					
22-60	42,5	0.04748 (0.02968; 0.067371)	0.06882	0.01021	7.38 seconds (30%)
> 60	57,5	0.04827 (0.03420; 0.062325)	0.10894	0.00094	6.55 seconds (24%)
PER MACHINE					
GEHC Discovery XR 656	47	0.04045 (0.02726; 0.055204)	0.06771	0.0132	8.28 seconds (30%)
Philips DigitalDiagnost	32	0.03414 (0.01860; 0.050987)	0.05283	0.01544	4.72 seconds (20%)
Carestream Health DRX-1	21	0.07419 (0.04843; 0.099508)	0.10677	0.04166	5.54 seconds (23%)
PER GENDER					
Male	51,6	0.03341 (0.01829; 0.050033)	0.06439	0.00244	8.84 s (32%)
Female	48,4	0.06885 (0.05025; 0.087271)	0.13118	0.00652	5.18 s (21%)

THE MRMC STUDY RESULTS

The study demonstrated an improvement in the performance of readers when aided by Rayvolve as measured by the AUC of the ROC:

- Reader AUC was significantly improved from 0.84602 to 0.89327 (a difference of 0.04725) across the 186 cases within Rayvolve's Indications for Use, spanning 13 study types (anatomic areas of interest) (p=0.0041)
- Reader sensitivity was significantly improved from 0.86561 to 0.9554.
- Reader specificity was improved from 0.82645 to 0.83116.

Rayvolve-aided and Rayvolve-unaided AUC (and sensitivity, specificity) result broken down by relevant confounders (gender,age, imaging device used to acquire radiographs).