

# CALCIVIS imaging system claims

This document outlines the overall logic flow of the claims that we make about our product and its potential utility. The claims are supported by published data in the literature and the Company's internal scientific and clinical programs (see Clinical Brochure that is used to support marketing in the UK and will be adapted for US marketing purposes in 2020).

## Indications for use

- The Calcivis Imaging System is intended to be used by dental healthcare professionals on patients (6 years and older) with, or at risk of developing, demineralization associated with caries lesions, on accessible coronal tooth surfaces.
- The Calcivis Imaging System is indicated for use to provide images of active demineralization on tooth surfaces, as an aid to the assessment, diagnosis and treatment planning for demineralization associated with caries lesions.

## 1. Caries process, demineralization and calcium ion levels

Caries process leads to tooth mineral loss due to dissolution caused by localized increased acidity associated with biofilm containing cariogenic bacteria.

Demineralizing enamel develops fluid filled pores as minerals are lost (initially between enamel rods, then whole rods are lost).<sup>1, 2</sup>

The fluid filled pores contain the products of dissolution, including free calcium ions.<sup>1, 3</sup>

Calcium ion concentration is elevated in the pores during active demineralization.<sup>4</sup>

The calcium ion concentration in the pores of an actively demineralizing caries lesion is relatively consistent over time i.e. it does not change significantly in response to short term changes in the lesion micro- environment such as eating or tooth cleaning.<sup>4</sup>

Active caries lesions (ICDAS definition) will have enamel pores with elevated calcium ion concentration (compared to inactive lesions or sound tooth surfaces).<sup>5</sup>

Inactive caries lesions (as defined by ICDAS) will be less porous due to surface remineralization.<sup>5</sup>

## 2. CALCIVIS proof of concept

CALCIVIS photoprotein (CP) produces light when it binds to calcium ions.

Luminescence level is directly proportional to calcium ion concentration.

Calcivis imaging system (CIS) can detect calcium ions on tooth surfaces/in enamel fluid filled pores.

CIS produces/detects luminescence from active caries lesions.

CIS does not produce/detect luminescence from sound tooth surfaces or inactive caries lesions.

CIS, used correctly, is detecting underlying hard tissue demineralization and not superficial biofilm.

CIS, used correctly, is not confounded by saliva/ambient light.

CIS images are not significantly affected by short term changes in oral pH.

### 3. Calcivis and lesion activity

***Definition: an active lesion is one in which there is ongoing demineralization (net mineral loss).*** <sup>6</sup>

Active caries lesions (as defined by ICDAS) are more likely to progress than inactive ones. <sup>5, 6</sup>

CIS can aid the clinician to differentiate active caries lesions from sound enamel and inactive caries lesions.

### 4. Calcivis System performance

Calcivis Imaging System has a high positive percentage agreement (PPA of 90.7%) and a high negative percentage agreement (NPA of 97.8%) between the images produced by the device and dentists' visual evaluation with ICDAS code for identifying active caries lesions (as determined by comparison with current best clinical practice). ICDAS 1 caries lesions were not evaluated in the clinical study to investigate the use of the Calcivis Imaging System.

CIS use is safe for adult and pediatric patients (6 years and above).

CIS is straightforward to use for the dentist health care professionals.

CIS can produce images effectively from all accessible coronal tooth surfaces (occlusal/free smooth).

CIS is effective at imaging lesions on primary and permanent teeth A CIS image takes less than one second to produce.

CIS images are compatible and readily uploaded by the most widely used image management software.

With appropriate training the CIS images are straightforward to interpret.

CP (dry powder) has a shelf life of at least 2 years (24 months) at room temperature (RT [at or below +25 °C]) CP (reconstituted) is stable for up to 2 weeks (refrigerated [+2 to +8 °C]).

#### 5. CALCIVIS imaging system positioning

The CIS enables dentists to capture and store images of tooth surfaces with labeled free calcium ions, consistent with demineralization in active caries, therefore providing an opportunity for implementation of strategies for caries management.

The CIS images do not, on their own, provide a definitive diagnosis of caries. They should be considered as part of the overall diagnostic work up and care planning for a patient.

The CIS also aids dentists in the assessment of the outcomes of preventive care by providing images of active demineralization on tooth surfaces.

The emerging consensus around a modern cariology curriculum in US and other dental schools provides a potentially supportive environment for the adoption of the CIS in general dentistry.

<sup>1</sup> Margolis HC1, Zhang YP, Lee CY, Kent RL Jr, Moreno EC, Kinetics of enamel demineralization in vitro, J Dent Res. 1999 Jul;78(7):1326-35.

<sup>2</sup> Robinson C1, Shore RC, Brookes SJ, Strafford S, Wood SR, Kirkham J, The chemistry of enamel caries, Crit. Rev Oral Biol Med. 2000;11(4):481-95.

<sup>3</sup> Carey CM1, Vogel GL, Chow LC, Permselectivity of sound and carious human dental enamel as measured by membrane potential, J Dent Res. 1991 Dec;70(12):1479-85.

<sup>4</sup> Vogel GL1, Carey CM, Chow LC, Gregory TM, Brown WE, Micro-analysis of mineral saturation within enamel during lactic acid demineralization, J Dent Res. 1988 Sep;67(9):1172-80.

<sup>5</sup> Amid I Ismail,1 Nigel B Pitts,2 and Marisol Tellez1, The International Caries Classification and Management System (ICCMS™) An Example of a Caries Management Pathway, BMC Oral Health. 2015; 15(Suppl 1): S9.

<sup>6</sup> Douglas A. Young, DDS, EdD, MBA, MS; Brian B. Nový, DDS; Gregory G. Zeller, DDS, MS; Robert Hale, DDS; Thomas C. Hart, DDS, PhD; Edmond L. Truelove, DDS, MSD; American Dental Association Council on Scientific Affairs The American Dental Association Caries Classification System for Clinical Practice A report of the American Dental Association Council on Scientific Affairs. JADA 146(2) <http://jada.ada.org> February 2015 79.



# CALCIVIS<sup>®</sup>

imaging system



Visualizing Active Demineralization

## CALCIVIS focus on dental innovation

The CALCIVIS imaging system will enable clinicians to **Visualize Active Demineralization** associated with caries, allowing for chair side, real time assessment.

The availability, for the first time, of visual evidence of active enamel demineralization supports a preventive approach to oral care.

## CALCIVIS history & people

CALCIVIS was co-founded in 2012. From its headquarters in Edinburgh, the CALCIVIS team combines product development, clinical and commercial expertise. The CALCIVIS imaging system was developed with input from leading international specialists in caries management.

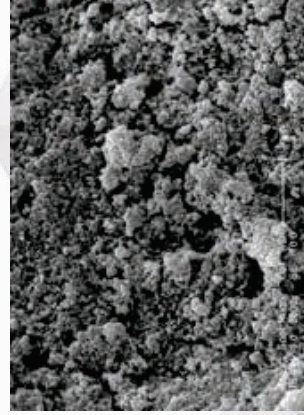




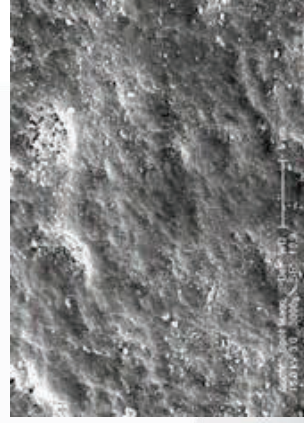
**Dental caries affects 1 in 3 of adults & 1 in 4 children despite being preventable<sup>(1)</sup>.**

### Enamel demineralization - the underlying effect of the caries process

Demineralization occurs as a result of localized acid from intrinsic or extrinsic sources. The loss of calcium leads to increased enamel porosity, widening of the spaces between the crystals and a surface softening allowing calcium ions to reach the surface through the widened pores.



Demineralized enamel (x 3000)



Sound enamel (x3000)

### Enamel lesions can be arrested and remineralized if identified early

ICDAS Dental Terms	Sound	First visual change in enamel	Distinct visual change in enamel	Localized enamel breakdown	Underlying dentine shadow	Distinct cavity with visible dentine	Extensive cavity with visible dentine
ICDAS Detection	0	1	2	3	4	5	6

Giving carious tissue the opportunity to arrest and remineralize is paramount. <sup>(2)</sup>

ICDAS <sup>(3)</sup> experts report that stage 1, 2 & 3 demineralized lesions can be arrested and remineralized if identified early making them ideal for preventive therapies and topical remineralization treatments and sealants.

### Only active lesions will develop into cavities

#### Which lesions are active?

Only active lesions will develop into cavities – identifying which to treat, has until the availability of CALCVIS imaging proved challenging.

Pit and Fissure sites
Buccal, Lingual and Palatal surfaces

R1: Oral Health Foundation: National Smile Month, Facts and Figures. Link: 26/8/16

R2: Banerjee, BDJ Vol 223 No3 Aug

R3: International Caries Detection and Assessment System.

## Visualize Active Demineralization

CALCIVIS enables dentists to visualize and communicate calcium loss, in real time from demineralizing enamel surfaces with the revolutionary CALCIVIS imaging system.

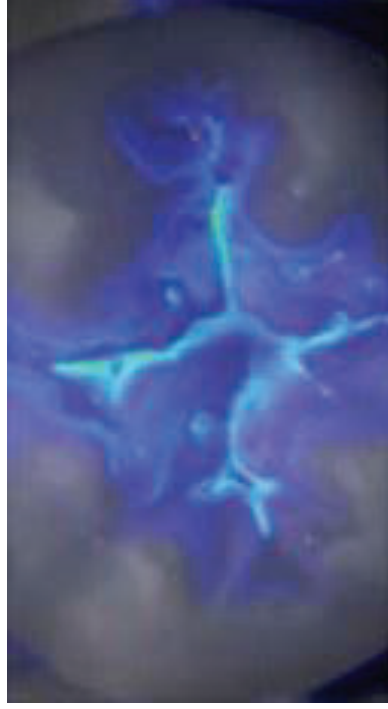


IMAGE: Typical example of a "demin-map" image as presented chair-side by CALCIVIS imaging system. (Areas of demineralization identified as lighter in color).

## Tell me, I'll forget. Show me, I'll remember

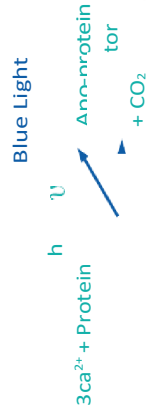
The easy to understand, on screen "demin-map" created within 1 second, by the CALCIVIS imaging system enables clinician to discuss surface changes chair side with patients. This discussion allows the clinician to engage patients in commitment to and compliance with prescribed Preventive treatments.



## At the heart of the imaging system is CALCIVIS photoprotein

### CALCIVIS photoprotein

CALCIVIS photoprotein is a dental biologic which produces a blue luminescence (light signal) in contact with free calcium ions. The luminescence is proportional to the level of free calcium ions at the tooth surface.<sup>(1)</sup>



Up to 10 patients can be imaged from one vial of CALCIVIS photoprotein.

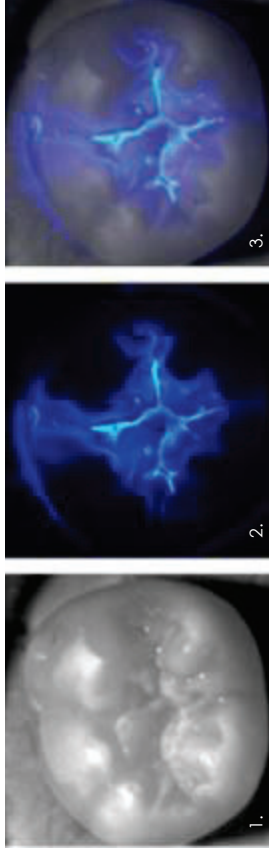


Up to 5 tooth surface can be imaged from one application of CALCIVIS photoprotein.

CALCIVIS imaging device applies CALCIVIS photoprotein and simultaneously images the resulting bioluminescence reaction.

## One touch process delivers chair side “demin map” image in <1 second

### CALCIVIS imaging sequence



Two images are captured in quick succession with one touch of the activation button. The first image is a visible one taken immediately before CALCIVIS photoprotein is applied (image 1).

A second image immediately captures the resulting luminescence (image 2).

Bespoke CALCIVIS software overlay the visible and luminescent images presenting them as an on screen “demin map” as bright areas of demineralization.



Is N., Melo P., Morfignion S. et al. Caries risk assessment, diagnosis and synthesis in the context of a European Core Curriculum in Odontology. Eur J Dent Educ 2011;15 (Suppl 1):23-31.

## Extensive scientific and clinical studies create reassurance

### Regulatory approval

The CALCIVIS imaging system is regulated as a CE marked Class IIa medical device in the UK and Europe.

### Performance and Safety testing

CALCIVIS technology has undergone extensive preclinical and clinical evaluation which demonstrate that the CALCIVIS imaging system can:

- Aid the clinician to differentiate active caries lesions, as determined by comparison with current best clinical practice, from sound tooth enamel<sup>(1)</sup>
- be used safely for adult and pediatric patients aged 6 years and above<sup>(2, 3)</sup>

## Clinical study completed using CALCIVIS imaging system

### Primary Analysis Agreement

Study ref	Type	Measure	N	Results*
NCT02780856*	Multi-center	1. Agreement between the expert clinician and independent GDP using CALCIVIS imaging system. 2. Patient and User feedback	110	1. Results meet the safety objective. No patient adverse events. Results meet Performance objective with statistically significant level of agreement ( $p < 0.0001$ ) <b>90.7% for active lesions (<math>p &lt; 0.0001</math>) for ICDAS 2 or 3</b>

**97.8% visible lesions ( $p < 0.0001$ ) for ICDAS 0**  
**ICDAS 1 teeth were not included in the clinical study**

2. Results show both patients and users consider the system useful and generally easy to use.

\*See CALCIVIS imaging system monograph for full details

### Secondary Analysis Agreement

Original Dentist	Agreement system		Independent Dentist	Calcvivis imaging
	N	n(%)		
ICDAS				
No visible lesion (ICDAS 0)	92	88 (95.7%)	p-value <0.0001	1-sided 97.5% CI Lower Bound 0.8924
Active lesion (ICDAS 2 or 3)	90	78 (86.7%)	<0.0001	0.7787
All teeth	182	166		

(1) ClinicalTrials.gov. Safety and performance evaluation of the Calcivis System. NCT02780856. Available at [www.clinicaltrials.gov/ct2/show/NCT02780856](http://www.clinicaltrials.gov/ct2/show/NCT02780856).

(2) Ormond C, et al. Safety and performance evaluation of the advanced prototype Calcivis caries activity imaging system. Poster at the 63rd European Organization for Caries Research (ORCA) Congress, July 2016, Athens, Greece. P105.





## Clinician feedback\*

### EFFICACY

*"Was able to confirm with a degree of confidence that there were no active caries in the teeth that were screened..."*

*"I was able to be more certain after imaging with the Calcivis system whether there was presence of caries in the teeth that were imaged"*

*"enables us to see small areas that can't be seen by eye or x-rays"*

### TIME SAVING

*"would save dentist time and prevent from making clinical mistakes"*

### ENGAGEMENT

*"I was able to demonstrate that to the patient"*

*"The patient understood more about preventive treatment and we were able to apply a fissure sealant that will prevent decay"*

*"The patient found the device very interesting and we had a discussion afterwards about dental erosion. It was very useful to motivate the patient to improve his oral hygiene"*

*"The patient's attitude towards dentistry changed. She was able to see clearly from the CALCIVIS image that there was a lesion present"*

*"Was able to demonstrate this to the patient and their parent"*



## Patient feedback\*

### ENGAGEMENT

*"We were very interested to see the images on the computer screen"*

*"I can't understand x-rays when I'm shown and could understand the photos. The fact that it can show up the lesion but not on the x-ray was very informative"*

*"I felt I learned a lot more about my teeth and thought the camera was brilliant not intrusive"*

*"I have never heard of demineralization before so was good to learn"*

### TIME SAVING, COMFORT

*"It was quick and comfortable"*

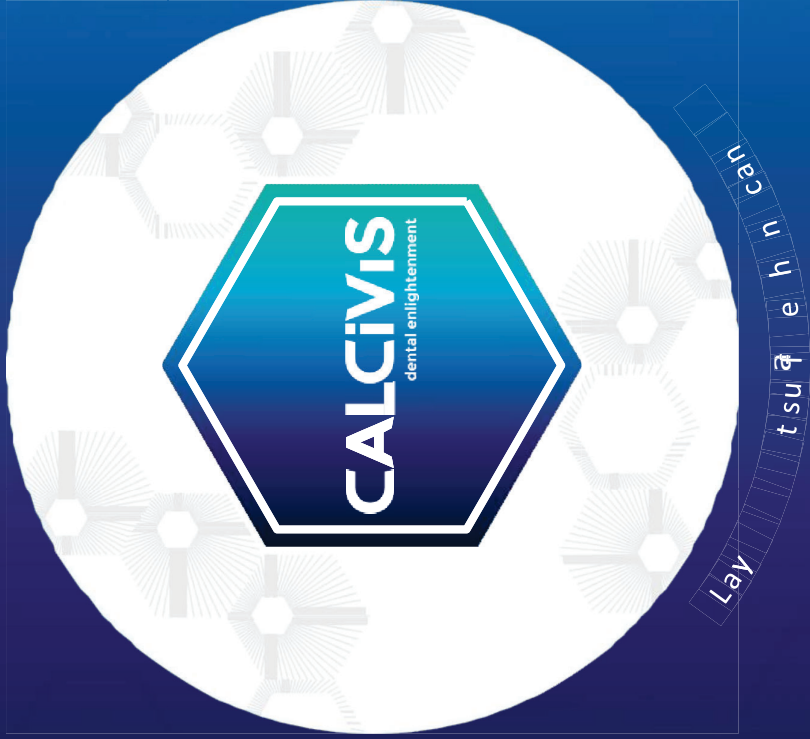
*"It was quick. It didn't hurt"*

*"It was painless and quick. I could see the pictures on the screen immediately"*

### VALUE

*"...with this I would be happy to pay"*

*"I don't understand why all dentists wouldn't have this..."*



# CALCiViS<sup>®</sup> imaging system

Download the CALCiViS  
augmented reality application  
and watch our unique  
augmented reality video.

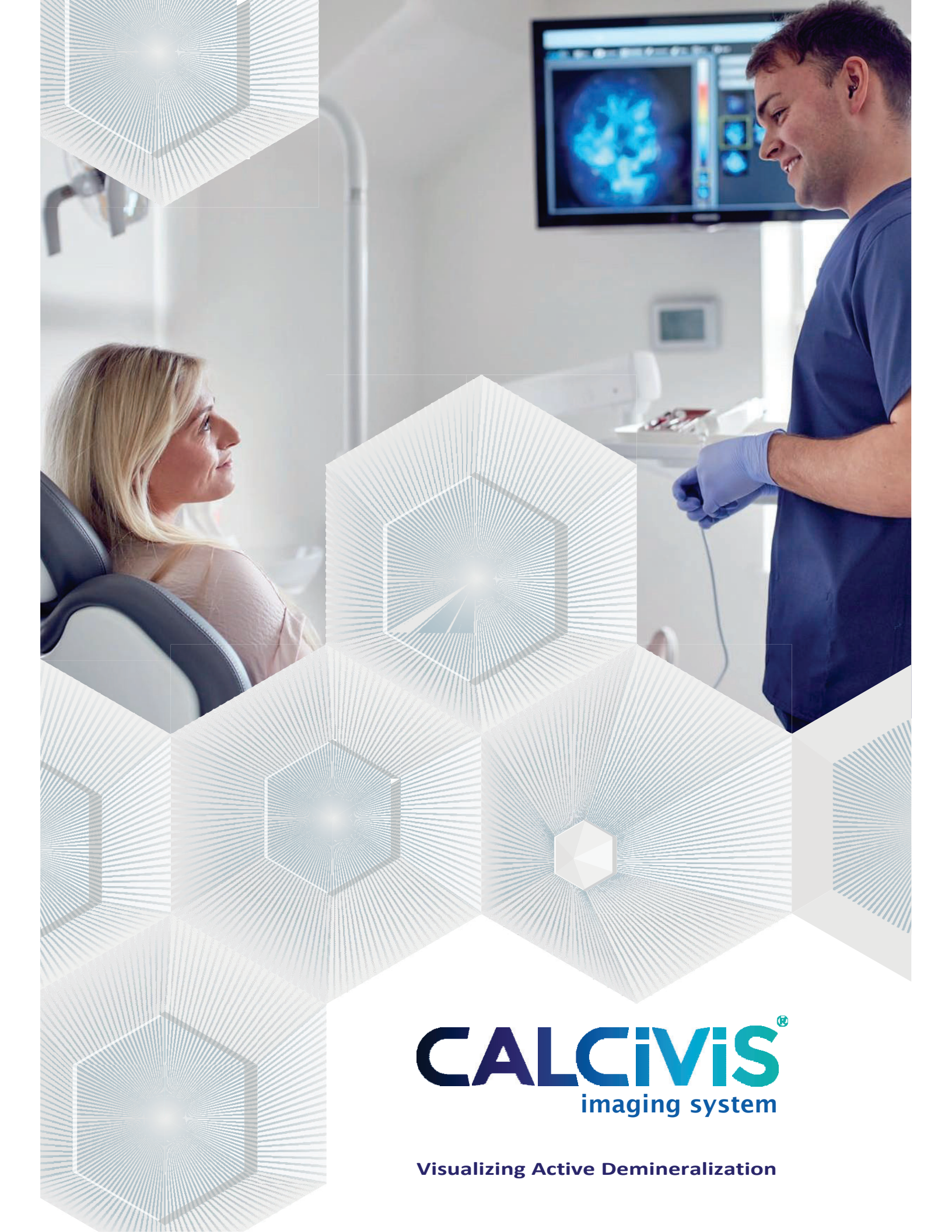
[www.CALCiViS.com](http://www.CALCiViS.com)



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**CALCIVIS<sup>®</sup>**  
imaging system

**Visualizing Active Demineralization**



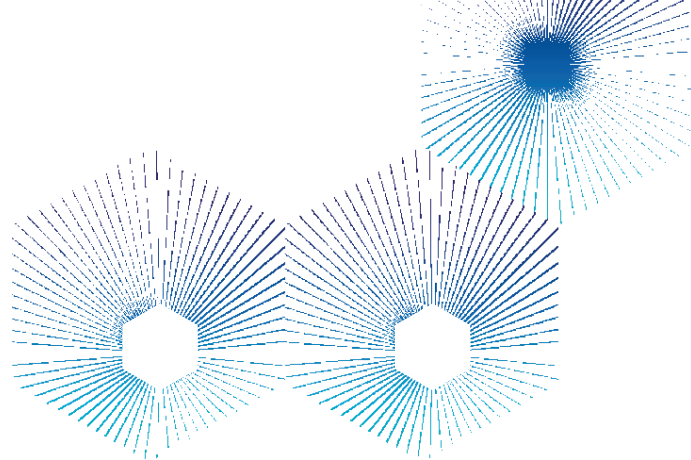
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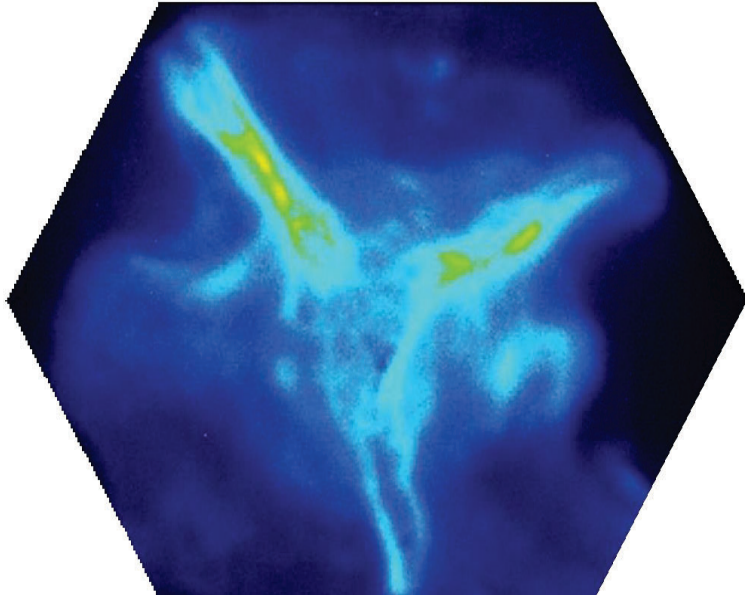
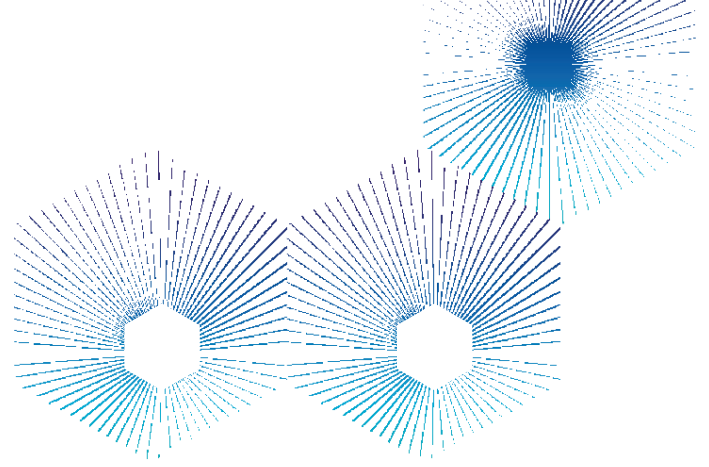


Figure 1. The CALCIVIS imaging system visualizes active demineralization of tooth surfaces, aiding the assessment of caries lesions.



## Background

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The system enables dental professionals to detect and visualize calcium ion loss from demineralizing tooth surfaces in the clinic.

The CALCIVIS imaging system represents the first use of biotechnology in dentistry. It uses a unique bioluminescent recombinant photoprotein which reacts with free calcium ions released from demineralizing tooth surfaces to enable early assessment of active demineralization due to caries. A specialized imaging device has been developed that applies the photoprotein on to the tooth surface and simultaneously images the resulting bioluminescent reaction. Early detection of demineralization associated with active enamel caries means that further progression to cavitation

involving the dentine can be arrested and reversed before restoration is required.

The CALCIVIS imaging system is a CE marked class IIa medical device in the UK and Europe and was launched first in the UK in the last quarter of 2017. The technology has undergone extensive preclinical evaluation. A pilot clinical study was completed in 2015<sup>1,2</sup> and a second, larger study finished in May 2017.<sup>3</sup> The latter study was designed to provide definitive clinical proof of concept for the CALCIVIS imaging system.

This document summarizes the science behind the CALCIVIS imaging system, the rationale for its use, the evidence supporting its safety and performance and how it should be used clinically.

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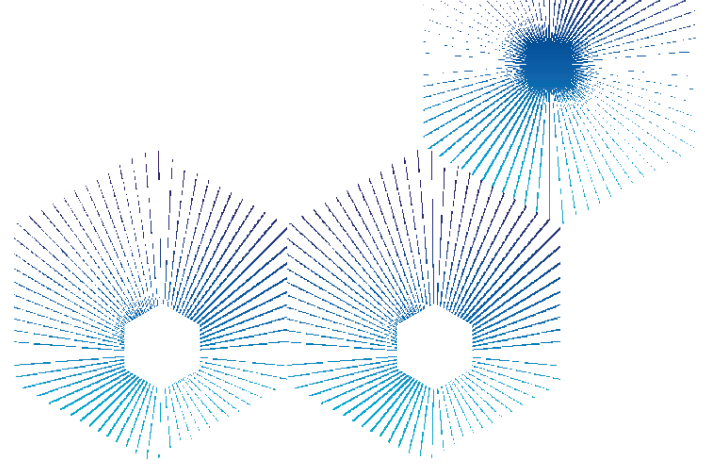
Figure 2. The CALCIVIS imaging device.



Figure 3. Dentists can observe active, demineralization of a tooth surface in real time during a routine patient consultation using the CALCIVIS imaging system.



# Demineralization, the caries process and calcium ions



The dental caries process leads to localized demineralization of the tooth surface, which may lead to progressive loss of tooth structure.<sup>4</sup> Demineralization occurs as a result of localized increased acidity associated with biofilms containing cariogenic bacteria. The loss of minerals leads to increased porosity, widening of the spaces between the enamel crystals and softening of the surface. This allows the acids to diffuse deeper into the tooth and dissolve out additional ions, such as calcium, hydroxyl and phosphate ions.<sup>4,5</sup> These ions reach the surface through the widened pores and diffuse into the plaque.

Once sugars are cleared from the mouth, the pH of the biofilm returns towards neutral and becomes saturated with free calcium, phosphate and fluoride ions so that demineralization stops and remineralization takes place. Caries lesions are therefore part of a dynamic equilibrium between the processes of demineralization and remineralization (Figure 4).

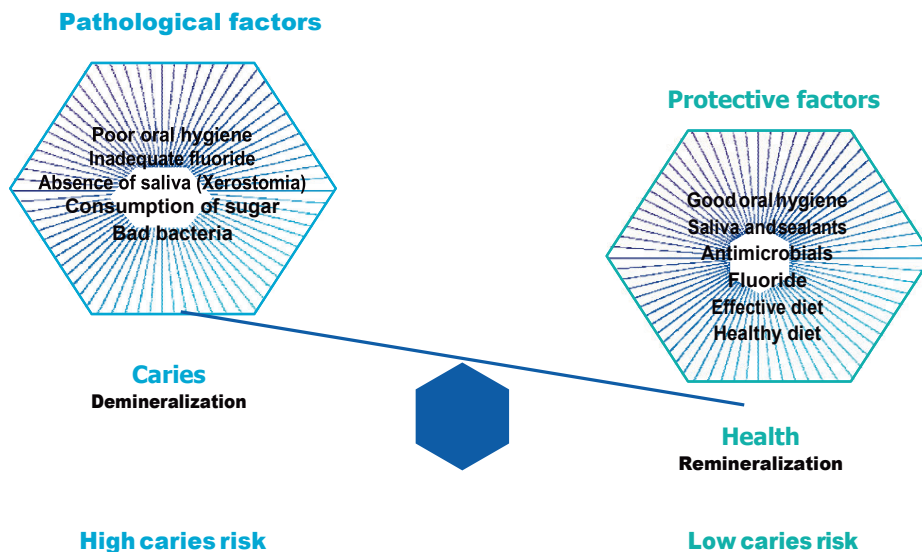


Figure 4. The balance of pathological and protective factors in the development of caries. <sup>Adapted from 4,6</sup>



The images in Figure 5 show that in sound (A) and remineralized enamel (C) there are fewer and smaller pores than in demineralized enamel (B) where the crystalline structure has broken down revealing fluid filled pores which will contain the breakdown products of hydroxyapatite (including free calcium ions).<sup>7</sup>

Calcium ion concentration is elevated in the pores during active demineralization, i.e. when demineralization is outstripping remineralization. In addition, the calcium ion concentration in the pores of an actively demineralizing caries lesion is relatively consistent over time, and does not change significantly in response to short-term changes in the lesion micro-environment, such as those induced by eating or tooth cleaning. Active caries lesions (as defined by the International Caries Detection and Assessment System [ICDAS]) that are subject to ongoing net demineralization will have enamel pores with elevated calcium ion levels compared to inactive lesions or sound tooth surfaces. In contrast, inactive caries lesions (as defined by ICDAS) will be less porous due to surface 'layer' remineralization.

As a result of the dynamic process, the very early, subclinical state of caries with non-cavitated lesions is reversible, allowing the possibility of arresting disease progression and remineralization (Figure 4).<sup>4,6</sup> Furthermore, an early diagnosis allows a decision to be made by the dentist and patient on the best course of action for their dental caries.<sup>5</sup>



***“As a result of the dynamic process, the very early, subclinical state of caries with non-cavitated lesions is reversible”***

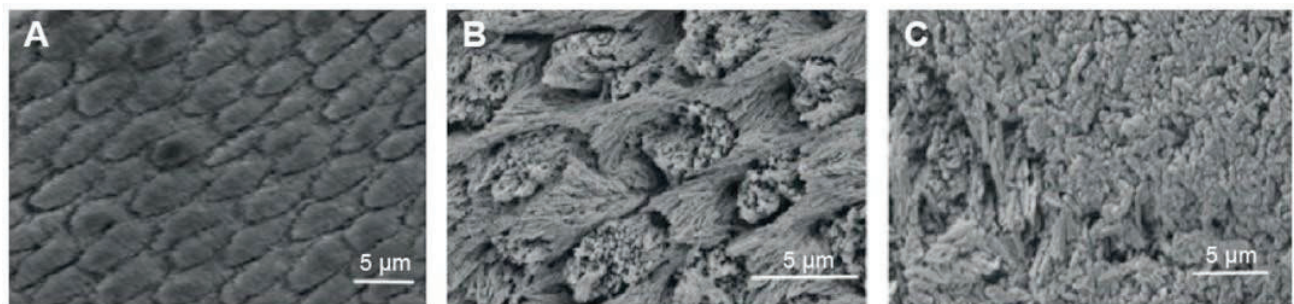
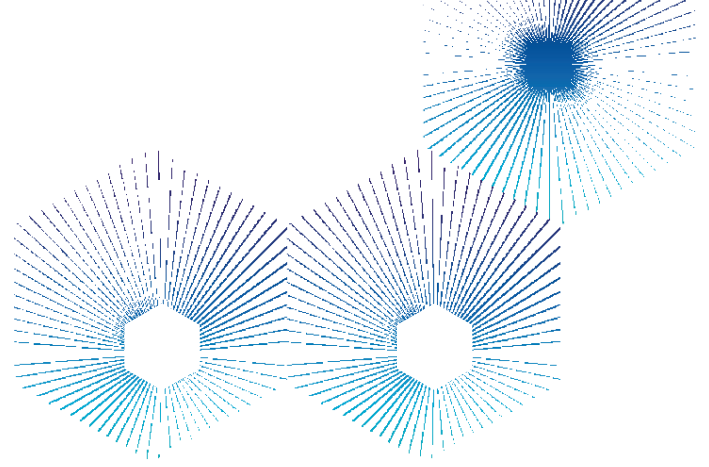


Figure 5. Scanning electron microscopic images showing (A) normal enamel; (B) enamel etched with phosphoric acid; (C) the recrystallized hydroxyapatite (HA) after solubilization (edges of the image) compared to unetched HA (center of the image). (Taken from Abou Neel EA et al. 2016 with permission<sup>7</sup>)

# Current management and the case for CALCIVIS technology



## Epidemiology of caries disease

Dental professionals are well aware of the prevalence of dental caries across the population. The latest NHS figures estimate that a third of 12-year-old children and nearly a half of 15-year-olds in the UK have visible evidence of tooth decay.<sup>8</sup> In adults, 31% have tooth decay.<sup>9</sup> Published data indicate between 55% and 95% of non-cavitated lesions on partially/fully erupted occlusal surfaces are considered to be active.<sup>10</sup> Given that caries disease is unequally distributed across the socio-economic spectrum,<sup>11</sup> it is disadvantaged communities (typically in developed economies 80% of caries are found in 20–30% of the population) that stand to benefit most from evidence-based caries management, particularly when assessments can be made at a single visit.



## Assessment of demineralization associated with caries

The assessment of active demineralization associated with caries remains a challenge, with no current available gold standard.<sup>12</sup> When a dentist detects an early ('white spot') caries lesion, technologies have not allowed the probability of progression to be determined.

The main detection and diagnostic aids for caries and demineralization have long been visual inspection and the use of a probe, together with X-ray images, relying heavily on subjective assessment and ongoing monitoring. There is a distinct lack of reliable diagnostic methods for detecting, measuring and monitoring the progress of carious lesions. The main issue with preventively treating dental caries is the difficulty in determining whether demineralization is taking place or not. In the current age of digital diagnostics where accuracy has been improved across a wide range of different medical fields, this type of educated 'guesswork' seems outdated.

***“In its early stages, demineralization associated with dental caries can be stopped and potentially reversed.”***

In its early stages, demineralization associated with dental caries can be stopped and potentially reversed. Timely diagnosis and prognosis are therefore critical to preventive management, eliminating the need for cavity preparation and restorative procedures.<sup>6</sup> Indeed, an editorial in the Journal of the American Dental Association emphasized the need for 'early detection and assessment of caries, before the macroscopic cavitation stage, to allow for secondary preventive treatments (fluoride varnish and remineralization therapies) to work and prevent progression of initial-stage caries'.<sup>13</sup> Diagnosis of early lesions is difficult, however, with current assessment methods missing 20–70% of pre-cavitated caries lesions.<sup>14</sup>





## How does the CALCIVIS imaging system improve preventive dentistry?

The CALCIVIS imaging system will, for the first time, allow the real-time detection and visualization of calcium ions released by active demineralizing caries in routine patient dental examinations. Early detection and assessment of caries activity with the CALCIVIS system enables tailored, rational, evidence-based treatment in line with dental best practice. It accelerates the ongoing development of preventive dentistry and moves away from the 'drill and fill' paradigm. The CALCIVIS imaging system provides information that informs lesion activity assessment in the ICDAS caries management process (Figure 6).<sup>15</sup>

*“The CALCIVIS imaging system will, for the first time, allow the real-time detection and visualization of calcium ions released by active demineralizing caries lesions...”*

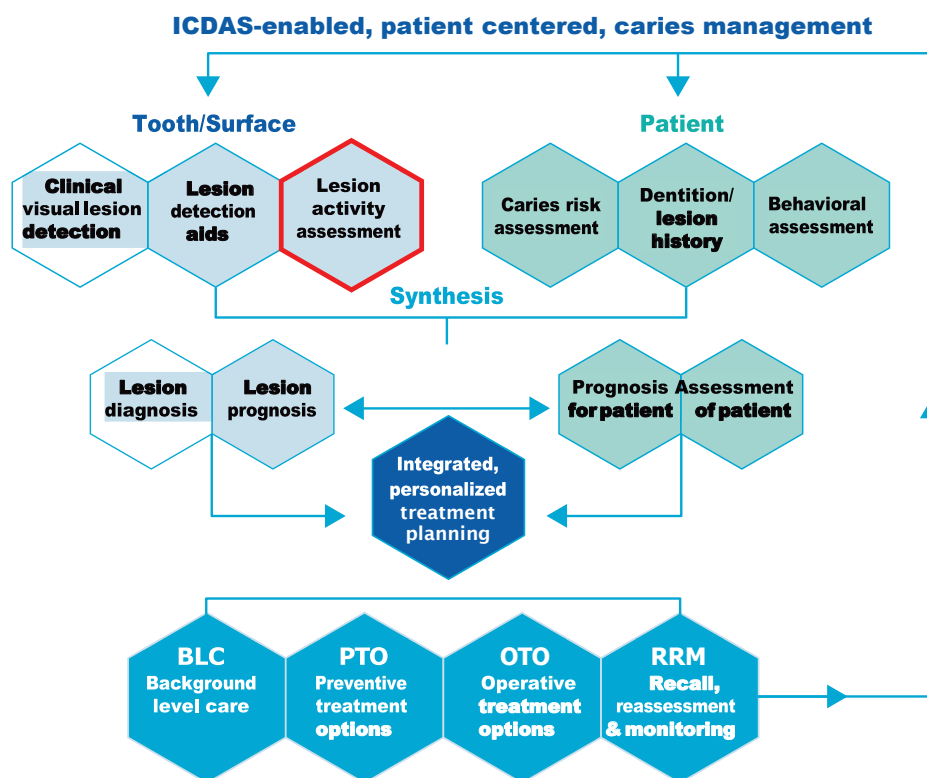


Figure 6. Overview of the ICDAS caries management process; the CALCIVIS imaging system provides information for the lesion activity assessment (red border). (Taken from Pitts N et al. 2011 with permission<sup>15</sup>)

## The CALCIVIS photoprotein and imaging system

At the heart of the CALCIVIS imaging system is the CALCIVIS photoprotein; a dental biologic which produces a blue light signal when it reacts with free calcium ions released at actively demineralizing tooth sites, proportional to the calcium ion concentration.<sup>16</sup> The CALCIVIS imaging system combines this bioluminescent marker and a sensitive intra-oral imaging device.

Initiated via a 'one touch' computer controlled process, a specialized integrated sensor immediately detects the resulting luminescence (light flash). In less than 1 second, bespoke software presents a chair side demineralization image to clinicians, enabling informed and efficient dialogue with patients.



*“CALCIVIS photoprotein; a dental biologic which produces a blue light signal when it reacts with free calcium ions released at actively demineralizing tooth sites”*



Figure 7. The CALCIVIS imaging system allows live visualization of active tooth demineralization, enabling a new standard of preventive care.

## Using the CALCIVIS imaging system

The CALCIVIS imaging system is intended to be used on visually accessible occlusal and free smooth surfaces and to provide the dental professional with additional information to the usual clinical visual and radiographic data in order to determine whether there is active ongoing demineralization associated with caries.



Figure 8. The CALCIVIS imaging system consists of a specialized intra-oral camera capable of imaging very low level, transient luminescence when a calcium-activated photoprotein is applied to enamel surfaces of teeth.

In normal operation, the dentist will identify the tooth surface of interest and after cleaning and drying will image a tooth using the CALCIVIS imaging device. The imaging is a fully automated 'one-touch' process whereby two images are taken in very quick succession. Initially a visible image is taken of the tooth surface with the LED light on. Immediately afterwards the LED switches off and CALCIVIS photoprotein is sprayed onto the surface under examination and a second image taken of the bioluminescence from the light

generated by the interaction between the CALCIVIS photoprotein and free calcium ions. The whole process takes less than a second. Software is used to overlay the visible and luminescent images to highlight regions where calcium ions are present, thereby providing demineralization maps of the tooth surfaces. Luminescence indicates areas of high active demineralization.

For full instructions on how to use the CALCIVIS imaging system, please see the Instructions for Use.<sup>17</sup>

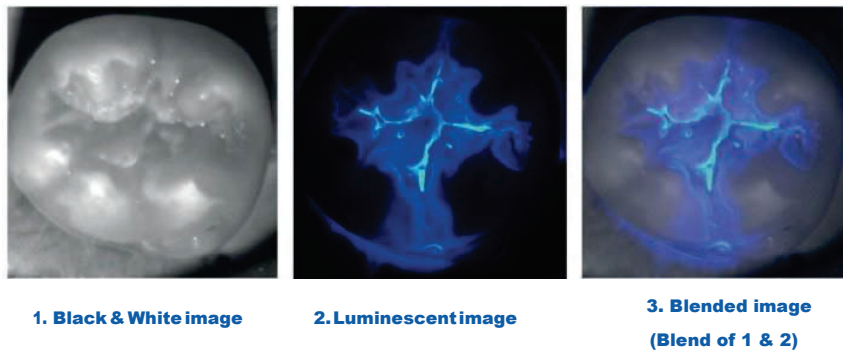


Figure 9. The CALCIVIS imaging system imaging sequence.

**Automated sequence – less than 1 second**

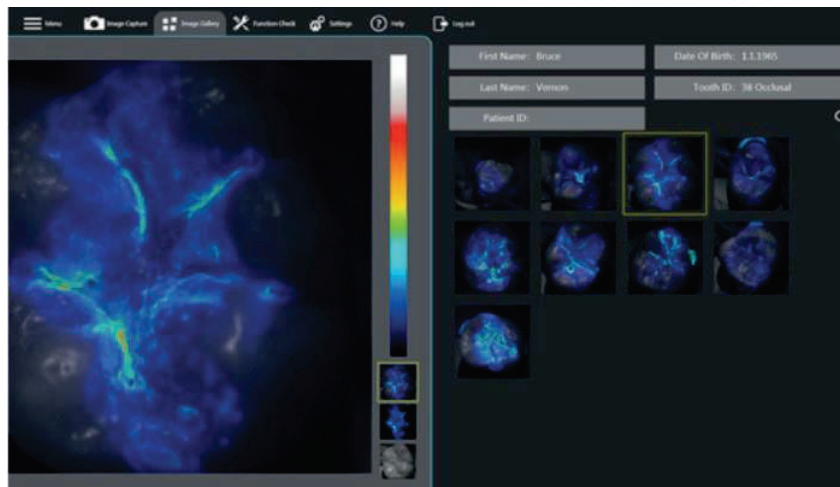
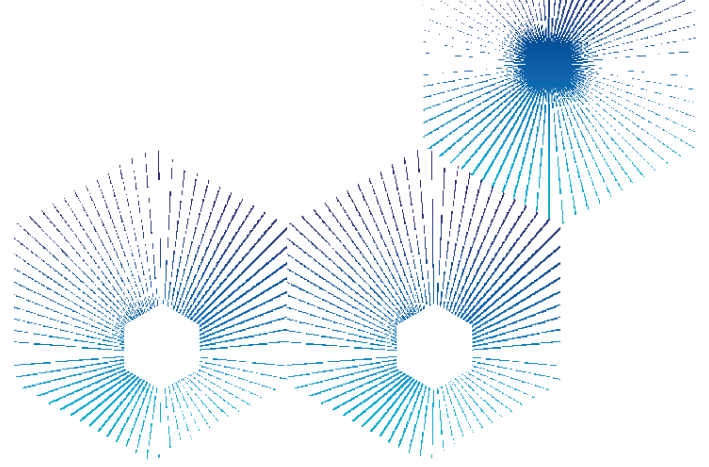


Figure 10. The CALCIVIS imaging system computer dashboard. The current session images are shown on the left-hand side and the previous images on the right, which supports dialogue and follow up.

# CALCIVIS imaging system safety and performance

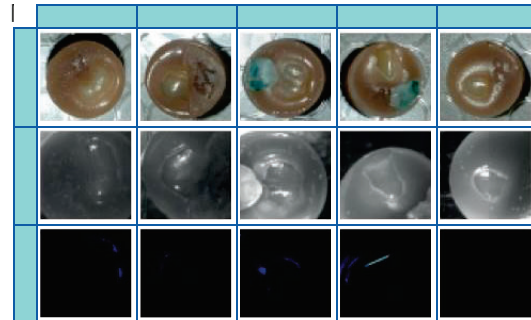


## In-vitro Experimental evidence

There have been a number of *in-vitro* experimental studies that support the clinical use of the CALCIVIS imaging system.<sup>5,12,18-21</sup> These studies have demonstrated that the CALCIVIS imaging system:

- can detect calcium ions in fluid-filled enamel pores of tooth surfaces<sup>21</sup>
- produces/detects luminescence from active caries lesions as correlated with the current methods (Figure 11)<sup>16</sup>
- does not produce/detect significant luminescence from sound tooth surfaces or inactive caries lesions (Figure 11)<sup>20</sup>
- detects *in-vitro* active demineralization in association with acid erosion with increased intensity of luminescence following further acid challenges (Figure 12)<sup>19</sup>
- agrees with visual criteria for lesion activity for permanent teeth<sup>5,16</sup>
- is not confounded by superficial biofilm following a simple cleaning protocol<sup>22</sup>
- images are not significantly affected by short term changes in the oral environment<sup>22</sup>
- is non-toxic, as shown by toxicology testing<sup>22</sup>

### Sound



### Active enamel caries

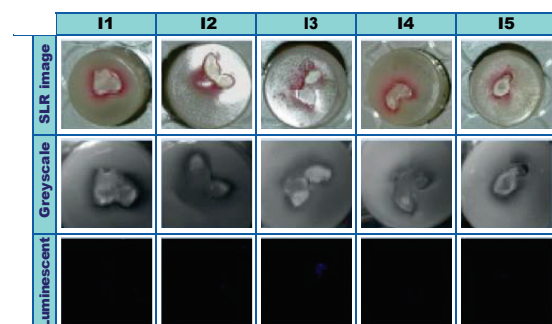
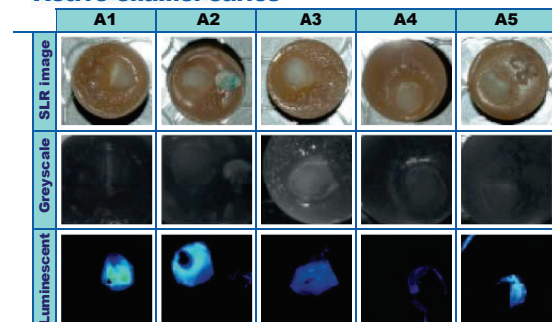


Figure 11. Evaluation of chemiluminescence for detection of enamel caries lesion activity.<sup>20</sup> Inactivated lesions were not luminescent, confirming the lack of demineralization within the lesion site. Sound teeth were also not luminescent.

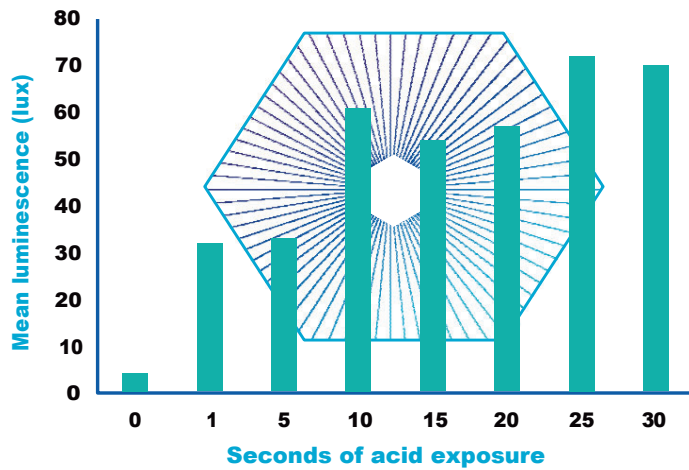


Figure 12. Mean luminescence successive acid challenge exposures of one set of five bovine enamel blocks to 30% phosphoric, which showed that luminescence increased in intensity.<sup>19</sup>

In an *in vitro* study of 46 extracted permanent posterior teeth (30 occlusal surfaces and 16 smooth surfaces), investigation sites were classified by two examiners using ICDAS<sup>23</sup> and Nyvad et al.<sup>24</sup> criteria for lesion activity.<sup>5</sup> The sites were also imaged using the CALCIVIS imaging system for the presence of lesion activity and the correlation among the three methods was calculated. There was a significant positive correlation between the CALCIVIS imaging system and the visual detection methods ( $p < 0.001$ ).

Table 1. Cross tabulation of activity assessment according to Nyvad et al.<sup>24</sup> and ICDAS<sup>23</sup> criteria and findings from the CALCIVIS imaging system.<sup>5</sup>

	ICDAS <sup>23</sup>		Nyvad et al. <sup>24</sup>		Total
	No	Yes	No	Yes	
No	4	1	5	5	5
Yes	1	40	41	0	41
N total	5	41	46	5	46

ICDAS, International Caries Detection and Assessment System

## Clinical studies of the CALCIVIS imaging system

There have been three main clinical studies of the CALCIVIS imaging system.<sup>1-3,25</sup> These studies have demonstrated that the CALCIVIS imaging system can:

- aid the clinician to differentiate active caries lesions, as determined by comparison with current best clinical practice, from sound tooth surfaces<sup>3</sup>
- be used safely for adult and pediatric patients aged 6 years and above<sup>1,2</sup>

## UK clinical study to evaluate performance and safety

This was a prospective, multi-site, non-randomized, study to investigate the use of the commercial version of the CALCIVIS imaging system

in the assessment of active demineralization of surfaces of teeth in patients aged  $\geq 6$  years (NCT02780856).<sup>3</sup>

The study's primary endpoints were to assess the safety and performance of the commercial CALCIVIS imaging system as measured by collection

of adverse events and by the correlation between the luminescent images and clinical assessment of caries lesion activity.

Five general dental practitioners from four dental practices across Scotland were involved in the study. At Visit 1, photographs were taken with a standard intra-oral camera and patients were then imaged with

the CALCIVIS imaging system. Patients returned at 7–14 days after Visit 1 for an oral examination. Images from each original dentist were independently reviewed

by another study dentist. A total of 110 patients were recruited to the study to obtain a total of 90 'sound' teeth and 86 'teeth with active lesions'.

There was a significant agreement between the original dentist and the independent dentist using the CALCIVIS imaging system for teeth with active lesions (90.7%;  $p < 0.0001$  for ICDAS 2 or 3) and sound teeth (97.8%;  $p < 0.0001$  for ICDAS 0).

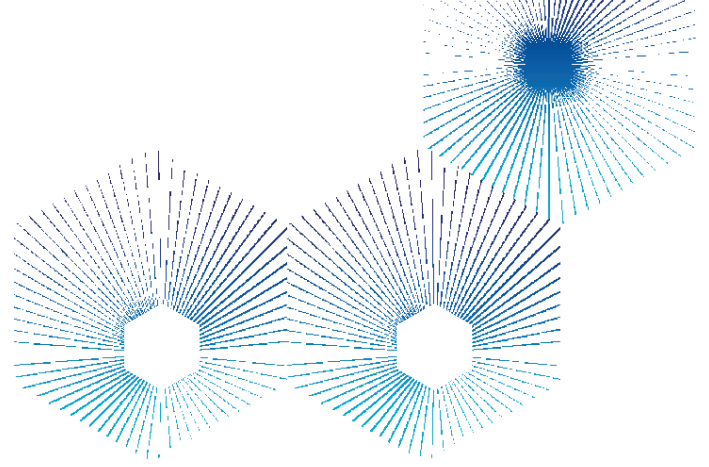
ICDAS 1 teeth were not included in the clinical study. There were no patient-related adverse events reported that were related to either the device or photoprotein.

Table 2. Overview of the CALCIVIS imaging system clinical trials.

Safety and performance evaluation of the CALCIVIS imaging system (NCT02780856) <sup>a</sup>	
Study design	Prospective, multicenter, open label involving five investigators at four UK general dental practices Two study visits
Patients	110 patients aged ≥6 years with one unrestored, accessible, free smooth buccal surface on a canine or incisor, away from the gingival surface identified with no visible lesions (ICDAS 0) and/or one unrestored, accessible, erupting or erupted molar or premolar with a visible lesion (ICDAS 2 or 3) in a plaque stagnation area Excluded patients: recent tooth bleaching (previous 2 weeks), ongoing re-mineralization treatment <sup>a</sup> ; fixed orthodontic appliance, currently taking part in clinical research or within previous 3 months; pregnant and/or nursing mothers
Primary outcome	1. Percentage agreement of sound/unsound teeth between ICDAS score and CALCIVIS imaging system 2. Collection of any adverse events
Results	<b>Agreement between the original dentist and the independent dentist using the CALCIVIS imaging system was significant for active lesions (90.7%; p&lt;0.0001 for ICDAS 2 or 3) and no visible lesions (97.8%; p&lt;0.0001 for ICDAS 0).</b> No patient-related adverse events were reported that were related to either the device or photoprotein Patients and users considered the CALCIVIS system to be useful and generally easy to use
<sup>a</sup> Includes, but not limited to, high concentration prescription fluoride toothpaste	



# Positioning of CALCIVIS imaging system in patient management



The CALCIVIS imaging system is a significant advance in preventive dentistry and is used in routine consultations to visualize, with your patient, early signs of active decay. This type of assessment has not been possible before and will give you an earlier opportunity to arrest or reverse demineralization, preventing future tooth structure loss. It enables you to practice enhanced preventive dentistry by aiding identification of active demineralization, treating the disease in its early stages. You will be able to explain, justify and demonstrate your diagnostic and treatment planning (and prevention of future pain and tooth loss). At each consultation visit, the patient will be able to visualize progress of their treatment which should help motivate them to continue and manage their disease. The value of your interventions will be clear to your patients.



The CALCIVIS imaging system should be used within a detailed care plan which will be dependent upon the individual patient situation and the dental practitioner’s preferred clinical approach. The system can be used

either on a site-specific basis such as ‘suspicious’ tooth surfaces, white spot lesions or possible active lesions, or otherwise on a screening basis as shown below:

*“The CALCIVIS imaging system is a significant advance in preventive dentistry and is used in routine consultations to visualize, with your patient, early signs of active decay.”*

Patient risk category	Tooth surfaces imaged
High (patients giving concern to their dentist)	Occlusal surfaces of all molars/ premolars (or site specific)
Low	Occlusal surfaces of lower/upper first molars (up to 4 teeth)



## Treatment when luminescent areas are detected

### Treatment:

Treatment is aimed at repairing enamel structures and helping to protect against further damage as follows:

- Active caries enamel lesion - requires arrest and remineralization (cleaning and 'painting'<sup>1</sup>) and management of the ongoing plaque challenge

Specific treatment actions will depend on the dental practitioner's personal practice and the individual patient situation. However, treatment algorithms that have been worked up in the International Caries Classification and Management System (ICCMS) and the Department of Health England 'Delivering Better Oral Health' guidelines provide useful guidance. An example of such guidance for children aged 7 or over and young adults is shown in the table.

### Luminescence signal

A luminescent area on an image indicates high levels of calcium ions in the region of the enamel generating the light signal. This is an indicator that the lesion is likely to be active and active lesions are more likely to progress. A luminescent area indicates that there is ongoing net demineralization at the point in time when the image is generated. So the images are an indicator of the likely probability of lesion activity and therefore an exact threshold value in terms of the light output is not relevant.

### DoH England:

#### Delivering Better Oral Health Guidelines

Specific guidance on prevention of caries in children aged from 7 years & young adults

Patients giving concern to their dentist

Fissure seal permanent molars with resin sealant

Apply fluoride varnish to teeth two or more times a year (2.2% Sodium Fluoride)

For those 8 years upwards with active caries prescribe daily fluoride rinse

For those 10+ years with active caries prescribe 2800 ppm fluoride toothpaste

For those 16+ years with active disease prescribe either 2800 ppm or 5000 ppm fluoride toothpaste

All patients

Apply fluoride varnish to teeth two times a year (2.2% Sodium Fluoride)

Investigate diet and assist to adopt good dietary practice in line with the Eatwell Guide

<sup>1</sup>Non-operative application of liquid/varnish/gel, such as fluorides or sealants, as distinct from operative drill/fill techniques.

## Patient benefits

Use of the CALCIVIS imaging system leads to increased patient involvement in the management of the disease processes. There is significantly more communication and engagement with the patient at each consultation visit as you can discuss the images on screen in a way that will be easy to understand. Where products such as fluoride varnishes, remineralization agents and sealants are being used to arrest or reverse active demineralization, patients can see their own treatment progress in real time. Innovations such as the CALCIVIS imaging system are changing dentistry and moving it away from the drill–fill paradigm, where relatively early lesions could often end up having a restoration. These developments are beneficial for patients. The CALCIVIS imaging system puts the focus on prevention combined with the use of secondary preventive products to increase patient motivation and compliance and ultimately improve the success of treatment.



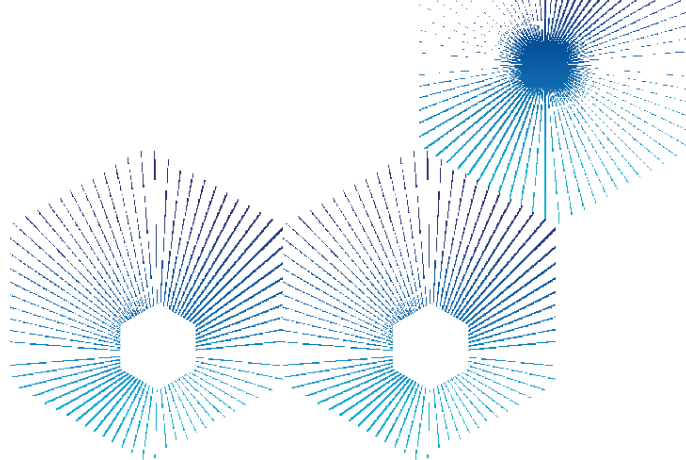
## Summary

The CALCIVIS imaging system is for the assessment of enamel demineralization due to caries. It is not appropriate for the diagnosis and treatment planning of advanced caries lesions which have cavitated into the dentine (ICDAS code 5 and 6) because these are clearly visible and usually require restoration. In a case where the dentist suspects dentine involvement in the absence of cavitation (i.e. ICDAS code 4, dentine shadow or 'hidden caries'), the dentist should rely on standard investigations for such lesions e.g. radiographic.

In summary, the CALCIVIS imaging system is a significant advance in preventive dentistry. It is the only technology available to assess lesion activity, providing an opportunity to arrest or reverse demineralization and prevent future tooth structure loss.

***"CALCIVIS is the only technology available to assess lesion activity, providing an opportunity to arrest or reverse demineralization and prevent future tooth structure loss."***

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- Section 7. Dismantling and cleaning
- Section 8. Maintenance and repair
- Section 9. Troubleshooting
- Section 10. Notes

# **1 CALCIVIS IMAGING SYSTEM: OVERVIEW**

The CALCIVIS imaging system is intended to be used by dental healthcare professionals on patients (6 years and older) with, or at risk of developing, demineralization associated with caries lesions, on accessible coronal tooth surfaces.

The CALCIVIS imaging system is indicated for use to provide images of active demineralization on tooth surfaces, as an aid to the assessment, diagnosis and treatment planning of demineralization associated with caries lesions.

The CALCIVIS Imaging System consists of two main components which are used in conjunction to enable a Dental Practitioner to obtain images of active demineralization on tooth surfaces: The CALCIVIS Imaging Device and the CALCIVIS imaging kit.

The CALCIVIS Imaging Device includes an intra-oral camera and associated software, which allows both video streaming of images and the capture of still images, and a mechanism which applies a small amount (25µl) of CALCIVIS photoprotein on to the tooth under investigation.

The key component of the CALCIVIS imaging kit is the CALCIVIS photoprotein which contains a non-therapeutic recombinant photoprotein which, in routine use, is applied at approximately 3µg per tooth with a maximum of 20 teeth (for example all molar and pre-molar occlusal surfaces) examined at any one visit.

The CALCIVIS Imaging System comprises:

## **1.1 CALCIVIS IMAGING DEVICE**

Consists of:

- CALCIVIS Intra-oral imaging device
- CALCIVIS Device cradle
- CALCIVIS (Imaging) Software on USB card
- CALCIVIS User Manual

## **1.2 ACCESSORY - CALCIVIS FUNCTIONAL CHECK KIT**

Consists of:

- CALCIVIS Functional Check Kit
- Instructions for use

## **1.3 ACCESSORY - CALCIVIS APPLICATOR MAIN BODY**

Consists of:

- Applicator main body
- Instructions for use

## 1.4 ACCESSORY - CALCIVIS IMAGING KIT

Consists of:

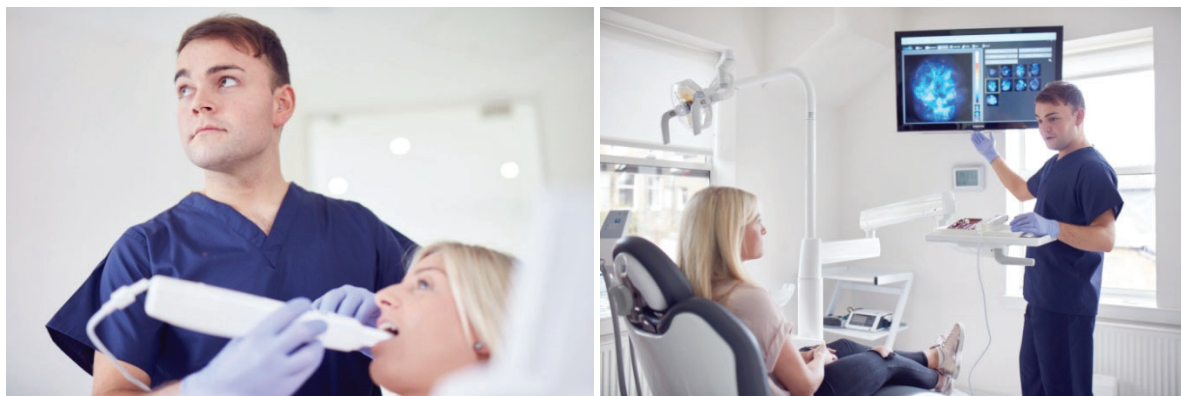
- CALCIVIS photoprotein (Freeze dried in vials)
- CALCIVIS diluent for reconstitution (containing 0.9% anti-microbial preservative Benzyl Alcohol)
- Vial Adaptors to allow for needle-less reconstitution
- Device syringes
- Medical wipes used to clean the top of the multi-use vial adaptor
- CALCIVIS applicator single use components
- Instructions for use

The photoprotein in the reconstituted CALCIVIS photoprotein solution binds with free calcium ions at the tooth surface and emits light (in visible spectrum) which is captured by the imaging system.

### Photographs of the product



*Figure 1 example photographs of device loading and fully assembled device on stand*



*Figure 2 example photographs of device in use*

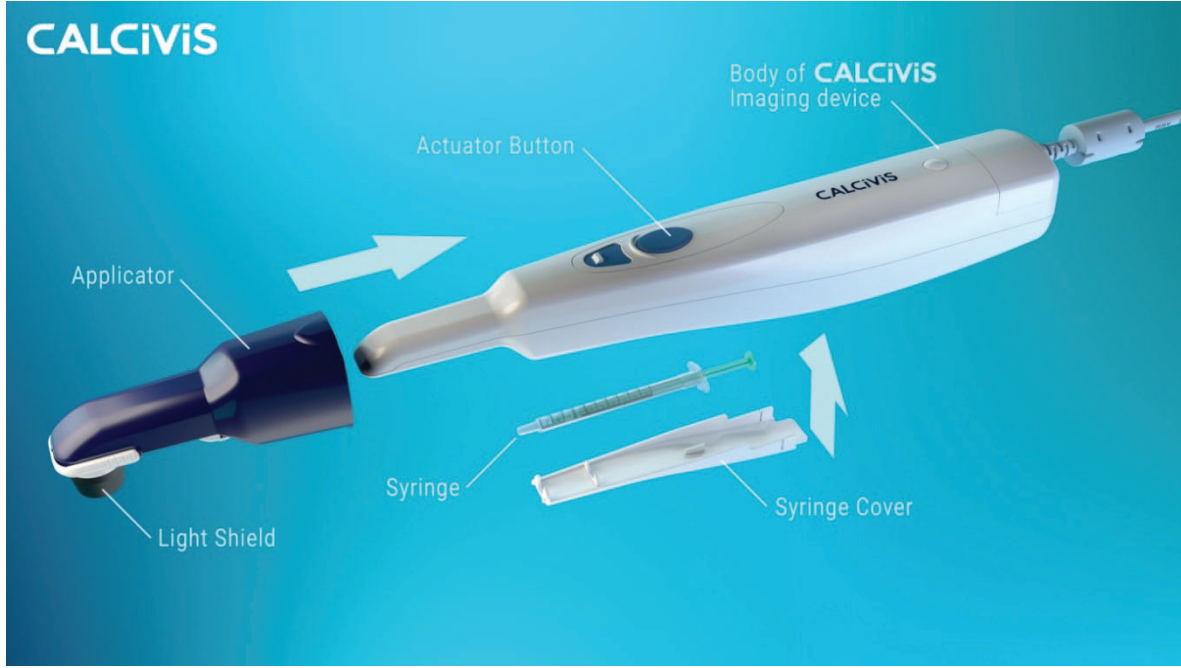
The CALCIVIS imaging system is indicated for use to provide images of active demineralization on tooth surfaces, as an aid to the assessment, diagnosis and treatment planning of demineralization associated with caries lesions. The CALCIVIS imaging system is for use by trained dental healthcare professionals.

The sequence of image capture and CALCIVIS photoprotein application are controlled using the custom application software. This also features the set-up of patient information within a database which allows sets of images to be captured. These are easily saved and a number of images can be compared for a number of patients over a period of time.












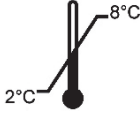

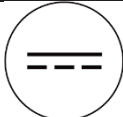



## 1.5 CALCIVIS IMAGING DEVICE: OVERVIEW

The picture shown below indicates the locations for the parts of the CALCIVIS imaging device which require the user to perform an action, and the component parts which will be removed and replaced after each set of assessments on individual patients have been completed.



## 1.6 SYMBOLS

The following symbols have been used on the system labels:

CALCIVIS imaging device Symbols			
	See instructions for use.		Lot number.
	Notified body CE mark.		Storage temperature limits.
	Manufacturer.		Expiry.
	Waste must be controlled according to local regulation and collection schemes for disposal of batteries.		SINGLE USE Do not re-use
	Device serial number.		Storage temperature limits.
	Warning/Caution		Direct current.
	Date of manufacture.		Type B applied part.
	Professional use only	IP42	Ingress Protection Rating

Operating temperature: 5 degrees C to 30 degrees C,

Humidity: 20% to 85% relative humidity, non-condensing

Storage temperature: Store away from sources of moisture below 35 degrees C

## 1.7 INDICATIONS FOR USE

The CALCIVIS imaging system is intended to be used by dental healthcare professionals on patients (6 years and older) with, or at risk of developing, demineralization associated with caries lesions, on accessible coronal tooth surfaces.

The CALCIVIS imaging system is indicated for use to provide images of active demineralization on tooth surfaces, as an aid to the assessment, diagnosis and treatment planning of demineralization associated with caries lesions.

## 1.8 CONTRAINDICATIONS

There are no known contraindications for the use of the CALCIVIS imaging system

## 1.9 WARNINGS AND PRECAUTIONS

### 1.9.1 GENERAL:

- The CALCIVIS imaging system should only be used in accordance with (CALCIVIS Instructions for Use and CALCIVIS User Manual).
- Read all the Instructions carefully before use. Failure to properly follow the instructions, warnings and precautions may lead to serious consequences or injury for the patient and user.
- The CALCIVIS imaging system should only be used by trained dental healthcare professionals.
- Do not use on patients with known sensitivities or allergies to photoproteins.
- Patients using recent tooth bleaching (within previous two weeks of treatment with the CALCIVIS imaging system) may affect quality of iamges.
- The CALCIVIS imaging system is an aid to the diagnosis and assessment of caries lesions and should always be used in addition to other methods of assessing caries (such as visual / tactile examination), before subsequent treatment planning.

### 1.9.2 ELECTRICAL SAFETY

- The CALCIVIS imaging device has been tested for compliance to IEC 60601-1-2:2015.
- Equipment connected to this product must conform to IEC standards (i.e. IEC 60601-1 for Medical electrical equipment, IEC 60950-1 for Information technology equipment, IEC 60065 for Audio, video and similar electronic apparatus). In addition, the combination and installation shall conform to IEC 60601-1. Any person who connects this product is responsible for ensuring that the system conforms to IEC 60601-1-1. To conform to IEC 60601-1, equipment connected to this product should be connected to the power supply via an isolation transformer and have at least basic insulation. For clarity; the Calcivis imaging device is powered via a **USB 3 port** of laptop or PC (not supplied with Calcivis imaging device kit).



WARNING: DO NOT PLUG THE CALCIVIS DEVICE DIRECTLY IN TO MAINS SUPPLY OR MAINS ADAPTOR.



WARNING: To protect the patient against the possibility of unwanted shock due to malfunction of the parent PC to the Calcivis intraoral camera via the USB3 cable, it is recommended the computer mains be connected to the Calcivis components using either a “medical isolation transformer”, or power the laptop using an IEC60601-1 conforming “medical grade power supply”.

When connecting to other devices, there is a risk that the leakage current may increase. If there is anything that you do not understand, please contact the dealer where this product was purchased.

### 1.9.3 ELECTROMAGNETIC INTERFERENCE AND EMISSIONS

- The EMISSIONS characteristics of this equipment make it suitable for use in industrial areas and hospitals. If it is used in a residential environment this equipment might not offer adequate protection to radio-frequency communication services. The user might need to take mitigation measures, such as relocating or re-orienting the equipment.
- Risk from electromagnetic fields. Electromagnetic fields might interfere with the functions of implanted systems (such as pacemakers).
- No modification of this equipment is allowed. This includes the USB cable. Only use the cable supplied with the device.  
Use of accessories, transducers and cables other than those specified or provided by the manufacturer of this equipment could result in increased electromagnetic emissions or decreased electromagnetic immunity of this equipment and result in improper operation.
- Do not modify this equipment without authorisation of the manufacturer.
- If this equipment is modified, appropriate inspection must be conducted to ensure continued safe use of the equipment.

#### 1.9.4 ELECTROMAGNETIC IMMUNITY



WARNING: Portable RF communications equipment (including peripherals such as antenna cables and external antennas) should be used no closer than 30cm (12 inches) to any part of the CALCIVIS imaging device, including cables specified by the manufacturer. Otherwise, degradation of the performance of this equipment could result.



WARNING: Use of this equipment adjacent to or stacked with other equipment should be avoided because it could result in improper operation. If such use is necessary, this equipment and the other equipment should be observed to verify that they are operating normally.

This equipment is intended for use in the electromagnetic environment specified below. The user of this equipment should assure that it is used in such an environment.

Immunity Against:	Compliance Level	Electromagnetic Environment
Radiated RF EM fields (IEC 61000-4-3: 2006 (+A1, A2))	3V/m 80-2700MHz Plus Proximity Fields	Power frequency magnetic fields should be at levels characteristic of a typical location in a typical commercial or hospital environment.
Power Frequency Magnetic Field 50/60Hz (IEC 61000-4-8:2009)	30A/m	

#### SYSTEM HARDWARE COMPONENTS

Physical Attributes	
Size (HxWxD)	30 cm x 5 cm x 4 cm
Weight	0.5 kg
Electrical Specifications	
Rating Voltage	DC 5 V
Power Consumption	0.9 W
Standby Power Consumption	0.1 W
Max Power Output	N/A
Environmental Specifications	
Temperature Range	Operating: 5°C (41°F) to 35°C (95°F) Storage: 0°C (32°F) – 40°C (104°F)
Relative Humidity	<95%
Protection Against Ingress of Water	IP42

### 1.9.5 SAFE ACCESS

- Not suitable for use if teeth cannot be accessed without causing trauma or upset to patients

There are several clinical conditions which could preclude the use of the CALCIVIS imaging system, in addition to many other dental instruments, devices and procedures, as they prevent the mouth opening wide enough to accommodate these devices, instruments and procedures. Such clinical conditions include:

- Radiation induced fibrosis – preventing mouth opening wide
- Scleroderma – skin hardening / tightening round mouth
- Medial pterygoid (masseter) muscle very strong - resulting in muscular pain and inability to open mouth
- Temporal Mandibular Joint (TMJ) disorder - when the disc moves forward at the mandibular joint preventing the amount the jaw can open
- Trismus (lockjaw) – reduced opening of jaw



### **1.9.6 CALCIVIS IMAGING DEVICE**

- Do not immerse the CALCIVIS imaging device in water – follow the Cleaning Instructions provided.
- The CALCIVIS imaging device should only be used with the cabling provided
- The CALCIVIS imaging device should only be used at the voltage stipulated
- Do not attempt to repair the product. Contact CALCIVIS if you have any concerns regarding the product

### **1.9.7 CALCIVIS KIT AND CALCIVIS PHOTOPROTEIN**

- Wear gloves
- Do not use the CALCIVIS kit if primary packaging has been breached in any way or is wet.
- Do not use the sterile syringe provided if the primary packaging has been breached in any way.
- Do not use the vial of freeze-dried CALCIVIS photoprotein or vial of CALCIVIS diluent if they have been damaged in any way or show signs of leakage.
- Do not fill the syringe with any solution other than the CALCIVIS photoprotein or CALCIVIS diluent.
- Always make up the CALCIVIS photoprotein according to the manufacturer's instructions.
- Once reconstituted CALCIVIS photoprotein should be stored refrigerated (2°C to 8°C); discard any unused CALCIVIS photoprotein after 2 weeks beyond reconstitution.
- The CALCIVIS photoprotein must only be used in conjunction with the CALCIVIS imaging system.
- Follow the instructions carefully for fitting the CALCIVIS applicator to the end of the CALCIVIS imaging device and check it is fitted correctly by gently pulling to ensure it does not dislodge.

## **1.10 ADDITIONAL INFORMATION**

Dental imaging examinations should be performed by a range of trained dental healthcare professionals. Interpretation of these results must be a matter for a specialist. The clinic needs to be suitably equipped and have staff capable of carrying out standard clinical procedures. Interpretation and reporting of the results should be done by a Dentist or a member of staff with suitable qualifications.

## **2 CALCIVIS IMAGING SYSTEM INSTALLATION AND SETTINGS**

Note: **As the video stream on the laptop or monitor is used to position the CALCIVIS imaging device over the teeth in-mouth it is important to ensure the viewing screen is clearly visible when using the device in the patient's mouth.**

**In addition, for best results avoid direct illumination of the mouth during the actual imaging process by ensuring the main overhead illumination lights are switched off.**

**It is recommended to turn sleep mode off on the PC or set it to >1hr as entering sleep mode may disrupt connection to the device.**

- **Unpack the CALCIVIS imaging system and place the CALCIVIS imaging device on the cradle provided.**

Note: **Always place the device on the cradle between uses. The device contains sensitive electronic and imaging components that can easily be damaged by heavy jolts such as dropping the device**

Note: **The Calcivis imaging system can be installed as either standalone (not integrated to other image management system) or regular (integrated to Software of Excellence ExaminePro Image Management System)**

### **2.1 MINIMUM SYSTEM REQUIREMENTS**

- **PC**
  - 2.0GHz processor, Intel i3 or better;
  - 4GB of RAM;
  - 200GB Hard Drive
  - 1366 x 768 or better screen resolution
  - Graphics card supporting at least DirectX 10 in hardware with at least 512MB video memory and supporting at least 24-bit colour
  - At least one accessible **USB 3** port
- **Operating System:** Windows 7 or 10
- **Available USB 3 port**
- **The CALCIVIS imaging device has been tested for compliance to IEC 60601-1-2:2015.**
- **Equipment connected to this product must conform to IEC standards (i.e. IEC 60601-1 for Medical electrical equipment, IEC 60950-1 for Information technology equipment, IEC 60065 for Audio, video and similar electronic apparatus). In addition, the combination and installation shall conform to IEC 60601-1. Any person who connects this product is responsible for ensuring that the system conforms to IEC 60601-1-1.**

To conform to IEC 60601-1, equipment connected to this product should be connected to the power supply via an isolation transformer and have at least basic insulation.  
For clarity; the Calcivis imaging device is powered via a **USB 3 port** of laptop or PC (not supplied with Calcivis imaging device kit).



**WARNING: DO NOT PLUG THE CALCIVIS DEVICE DIRECTLY IN TO MAINS SUPPLY OR MAINS ADAPTOR.**



**WARNING:** To protect the patient against the possibility of unwanted shock due to malfunction of the parent PC to the Calcivis intraoral camera via the USB3 cable, it is recommended the computer mains be connected to the Calcivis components using either a “medical isolation transformer”, or power the laptop using an IEC60601-1 conforming “medical grade power supply”.

When connecting to other devices, there is a risk that the leakage current may increase. If there is anything that you do not understand, please contact the dealer where this product was purchased.

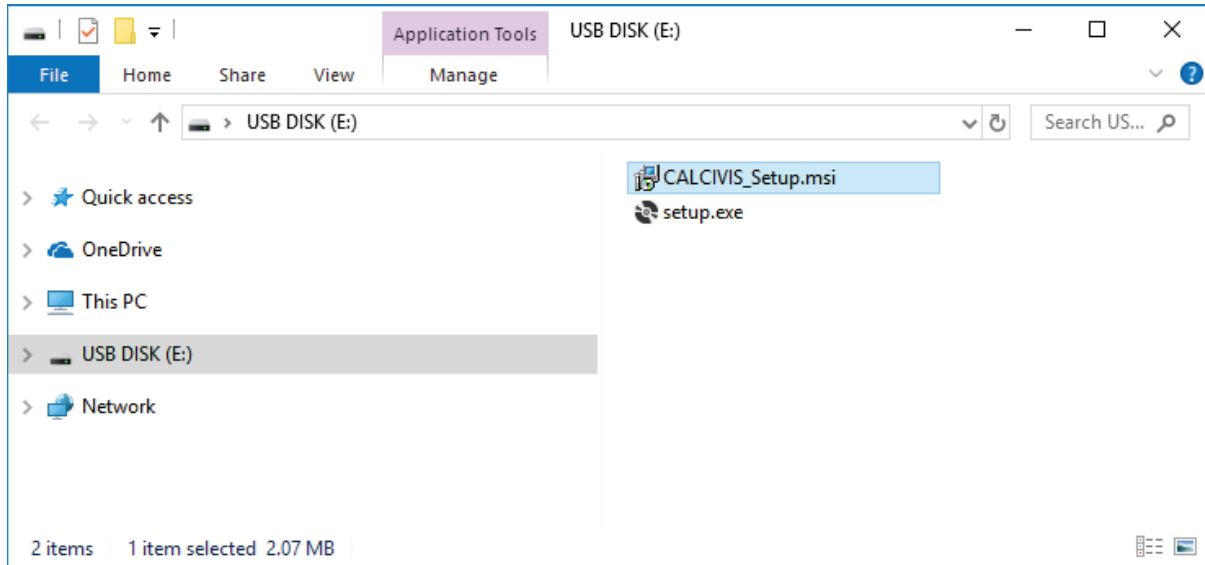
### **About Cybersecurity**

CALCIVIS imaging device can be installed on regular Windows PCs (Operating System Windows 7 or 10). The operating institution is responsible for installing antivirus software and a firewall on the PC, for installing critical Windows updates regularly, and for keeping the PC otherwise secure.

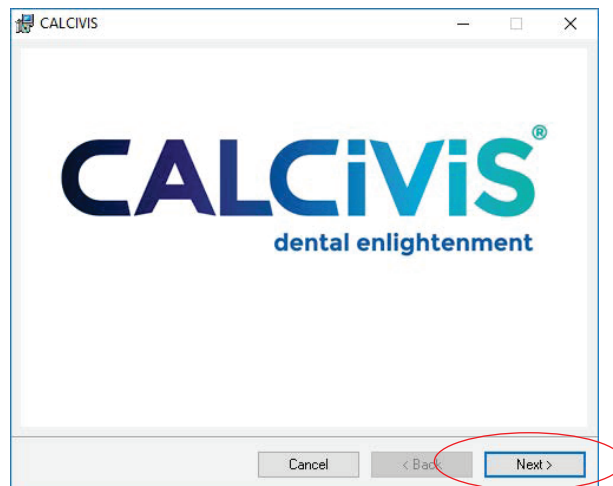
CALCIVIS imaging device itself is not directly connected to the network. CALCIVIS imaging device can be connected to a network via a PC/laptop for various purposes but can also function stand-alone without network access. No Patient data is held on the firmware of the device or the application software, only images are created that are then used by the operating institution.

## 2.2 APPLICATION INSTALLATION INSTRUCTIONS

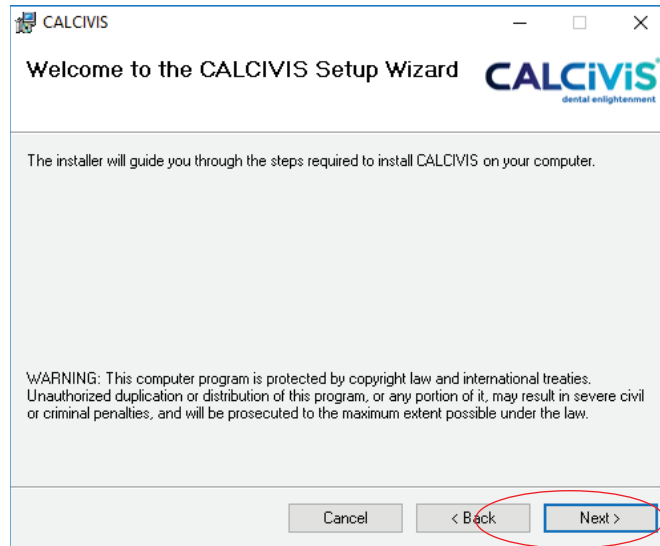
- Ensure all other programs are closed before starting installation.
- Insert the CALCIVIS application software card into any available USB port and navigate to the USB card folder.
- Double-click the setup.exe file to run the installer.



- The following window will appear. Click 'Next'.

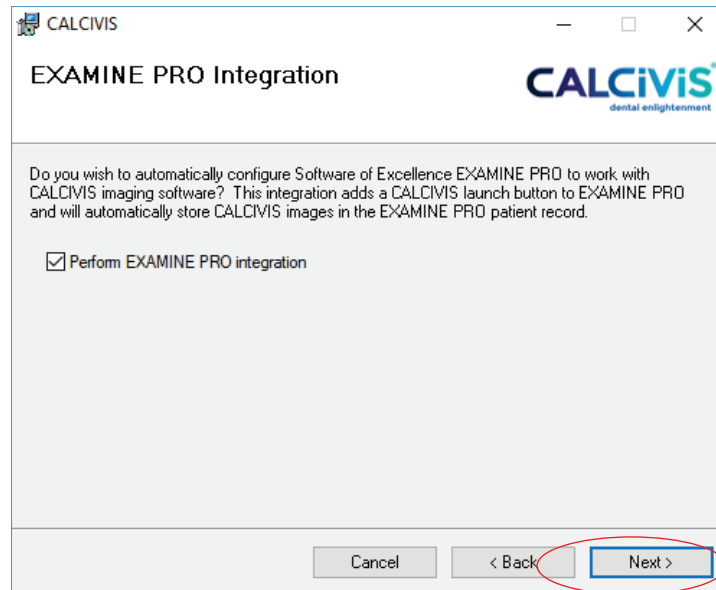


- The following view will appear. Click 'Next'.



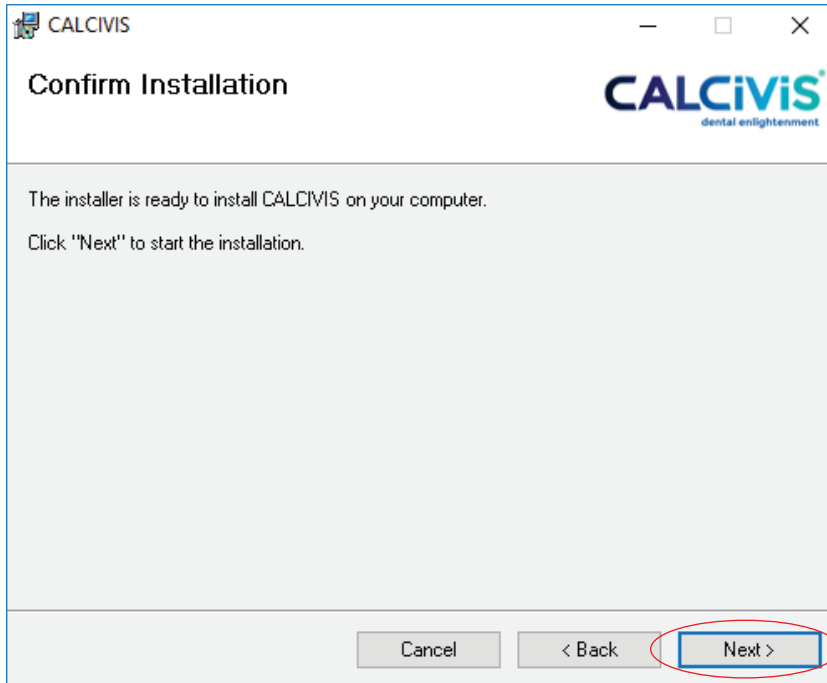
- The following view will appear. If you wish to install the optional Examine Pro integration, allowing the CALCIVIS app to be launched within Examine Pro and the images to be stored within its patient record, ensure 'Perform EXAMINE PRO integration' is selected and then click 'Next'. This will be selected by default.

**Note: Examine Pro MUST be installed before installing the CALCIVIS software.**

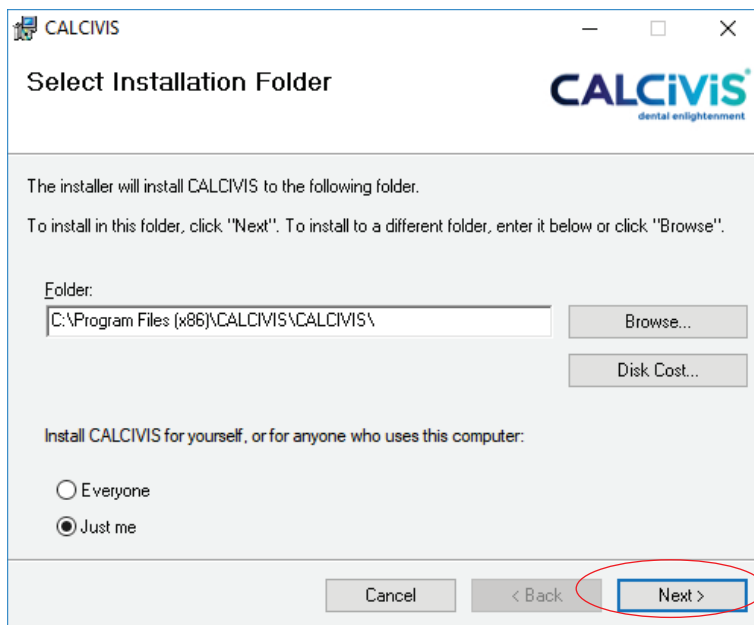


If you do **NOT** wish to install the Examine Pro integration, deselect this option and click 'Next'.

- The following view will appear. Click 'Next'.



- The following view will appear, allowing you to select where the installed application will be stored. The default folder (on a 64-bit machine) is C:\Program Files (x86)\CALCIVIS\CALCIVIS. If you want to install the App in a different file location select 'Browse...' and navigate to the desired file location.

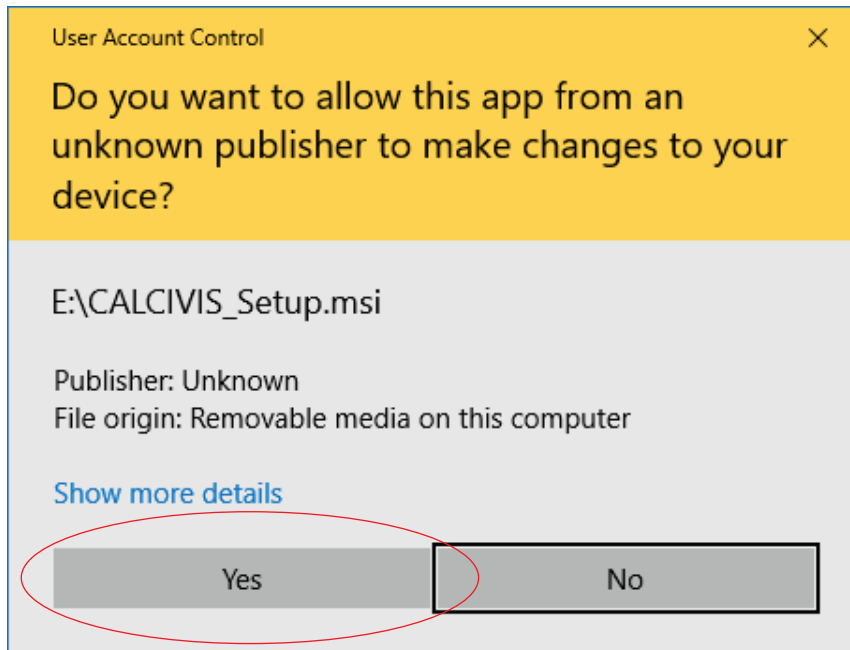


- If you wish to install the application for use on all user accounts on your PC, select 'Everyone'. If you only want to install the application on the current users account, select 'Just me'.

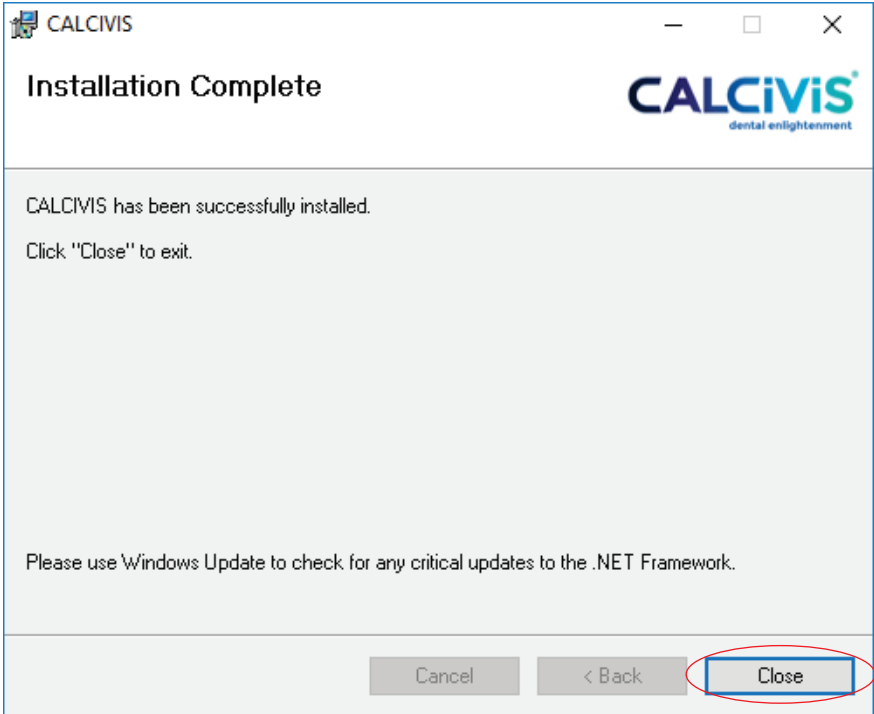


'Just me'. This option will be selected by default. When you have selected the desired settings, click 'Next'.

- The following User Account Control pop-up warning may appear. If so, click on 'Yes'.



- Installation is now complete, click on 'Close' to finish. A shortcut to the CALCIVIS app will now appear on your desktop and start menu.



## 2.3 STARTING THE CALCIVIS APPLICATION

Connect the CALCIVIS device by plugging into a **USB3 port**. Check the port is USB 3 (USB3 ports are identified by this symbol  and/or blue colouration inside the port). The LED lights should flash 3 times and the mechanism move to its home position.

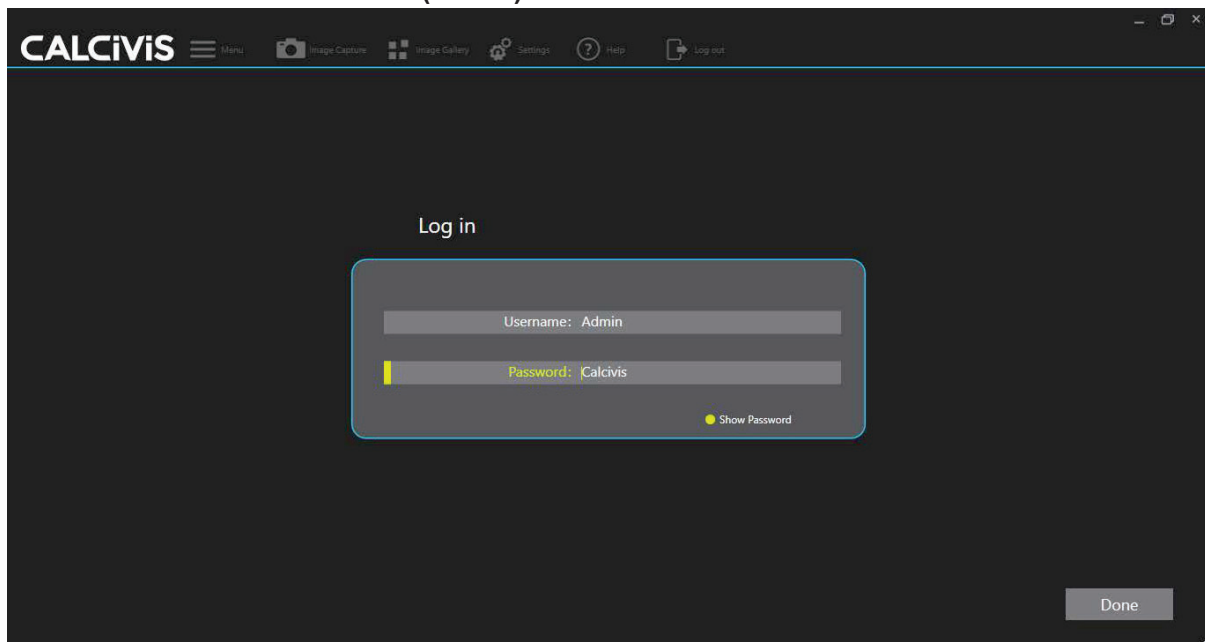
**Note: Ensure device is powered on and connected prior to starting application to avoid error message.**

To start the application, double click on the CALCIVIS application icon:



The application will start, and the **Welcome** (login) screen will be displayed.

### 2.3.1 THE WELCOME SCREEN (LOGIN)

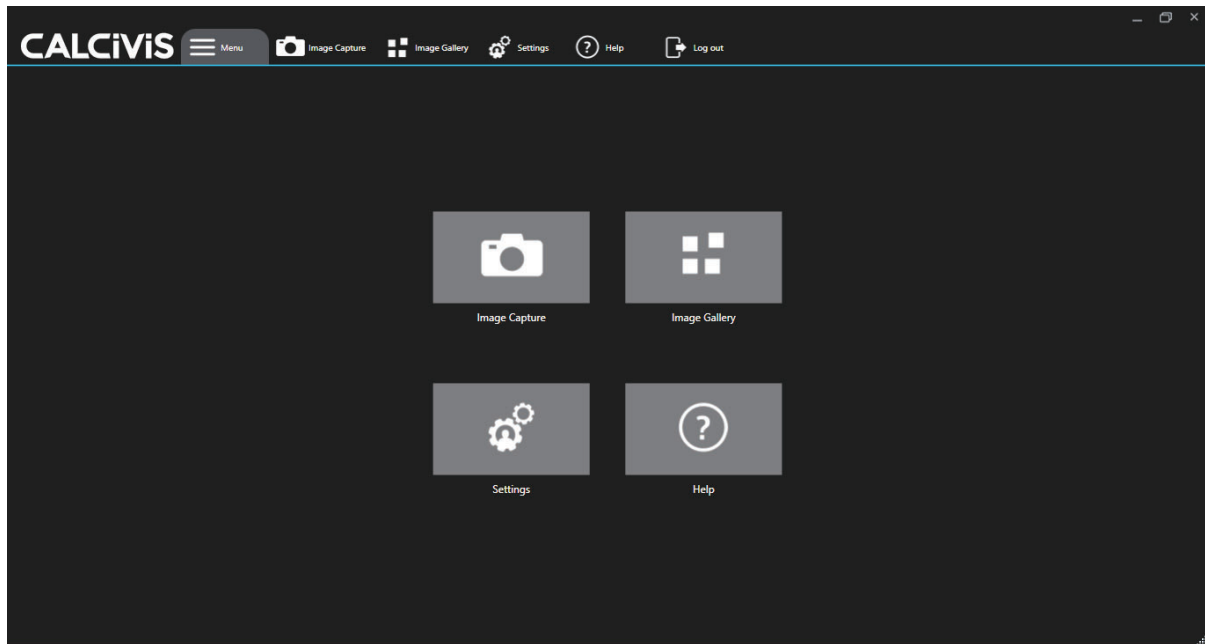


The Welcome screen allows authorised users to logon to the CALCIVIS application.

On first use logon to the application as administrator:

- Enter user name: Admin
- Enter password: Calcivis
- Click on **Done** when ready

## 2.4 WELCOME SCREEN AND NAVIGATION BAR

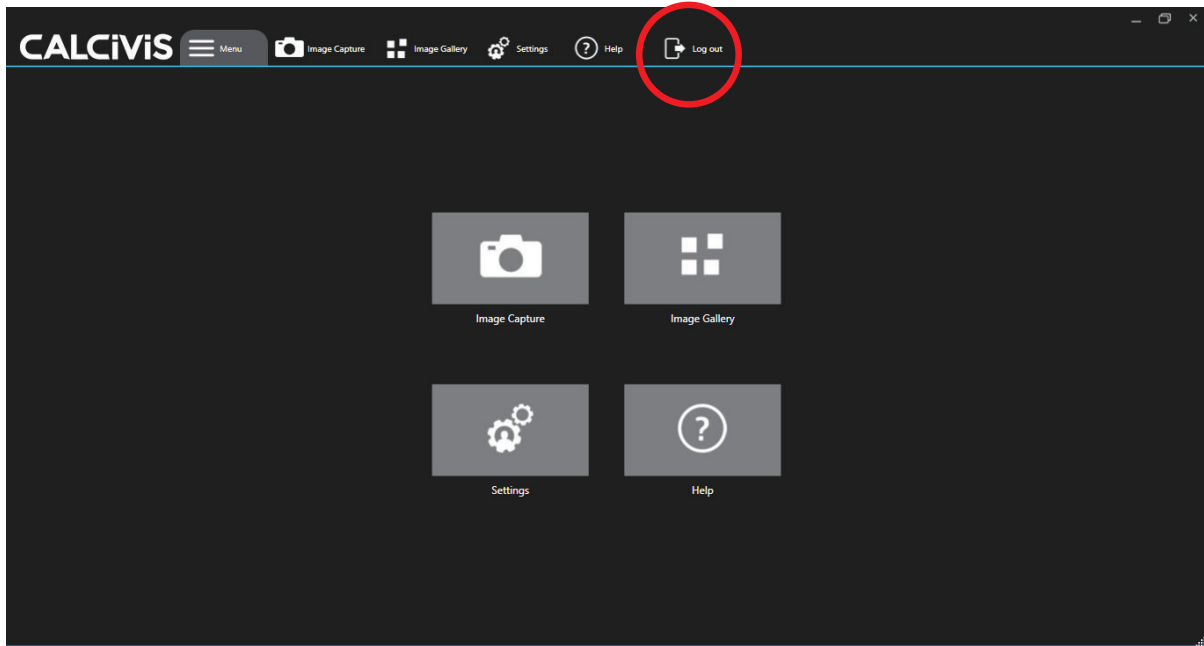


The Navigator bar appears along the top of each of the screens and enlarged icons appear on the screen immediately after login.

It allows the user to select which of the screens to display:

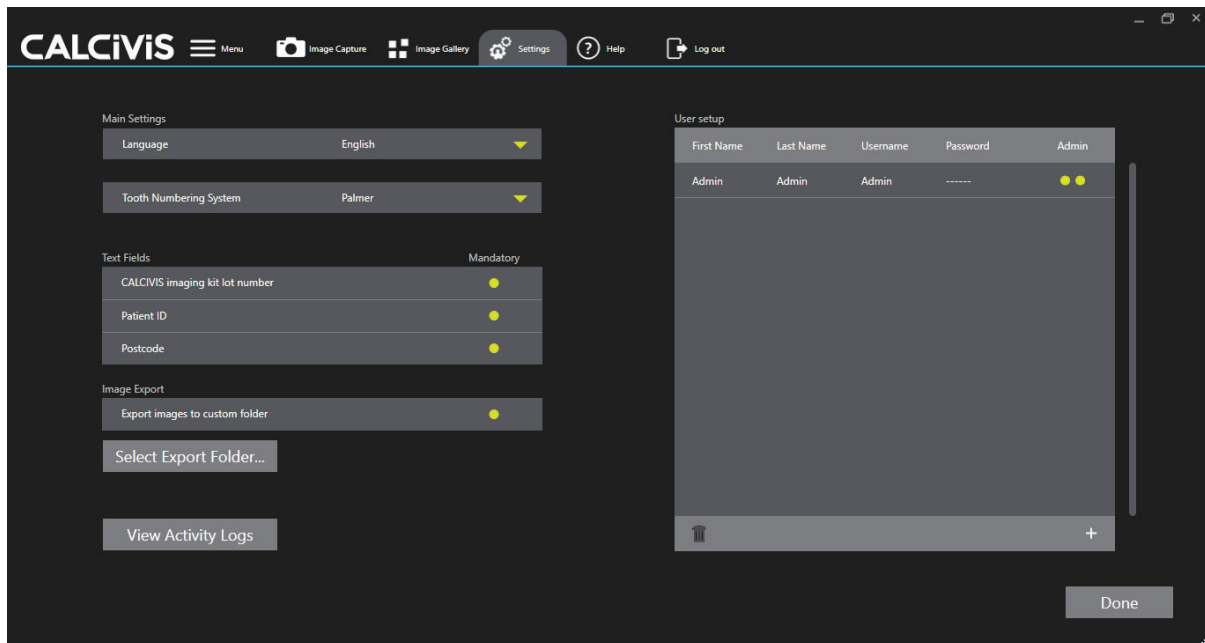
- Image capture
- Image Gallery
- Settings
- Help
- Log out

## 2.5 LOGOUT



To logout from the CALCIVIS application, the user should click on **Logout**.

## 2.6 THE SETTINGS SCREEN



### 2.6.1 APPLICATION SETTINGS

The settings screen is an area for users with Administration rights only where users can be assigned passwords and various software settings can be selected.

Main settings allow you to choose from drop down boxes:

- Language
- Tooth numbering system.

Text fields allow you to determine which patient details are mandatory

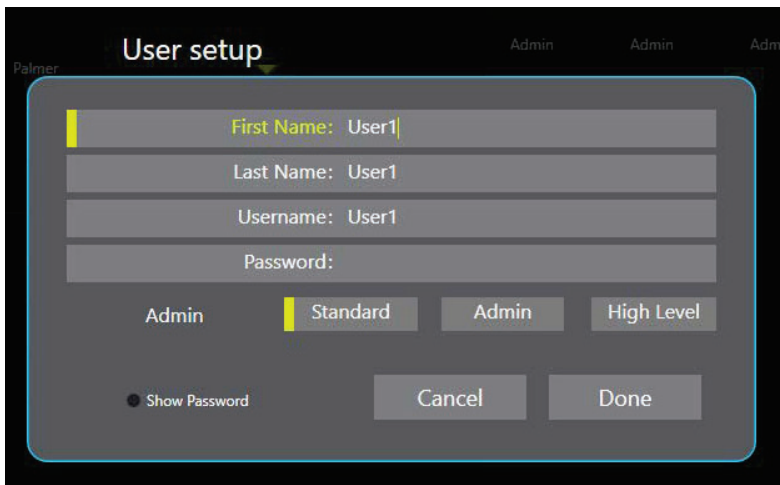
Image export allows you to select a folder to export a copy of all images to for use outside the CALCIVIS software.

Activity log may be required by CALCIVIS technical support and can be accessed by clicking the 'View Activity Logs' button



## 2.6.2 USER SETUP

- New users are added by clicking the '+' symbol. The user setup dialogue box will appear. Complete all fields and click done.



- To delete a user, select the user and click the trash icon. Note: you can not delete the user that is currently logged in.
- To edit a user double-click the user. The User setup dialogue box will open allowing details to be updated.

## 2.6.3 PASSWORDS

Users can use a combination of user name and password in order to control access to CALCIVIS imaging device. It is the responsibility of the operating institution to apply the appropriate password policies (for example, password strength and password renewal intervals). CALCIVIS imaging device does not include functionality for password strength and password expiration requirements. In case user handling is deactivated a default, password is used to restrict access to certain functionalities. Follow these general recommendations on password strength in case your institution does not have a more specific policy:

- Use a minimum password length of 8 characters.
- Include lowercase and uppercase alphabetic characters, numbers and symbols.
- Generate passwords randomly where feasible.

Follow this general recommendation for a password renewal interval in case your institution does not have a more specific policy:

- Passwords should be renewed after 90 days.

**Note: It is advisable to change the Admin Password to avoid non-administrators accessing editing rights in settings**

**For continued secure use, perform Windows software updates regularly**

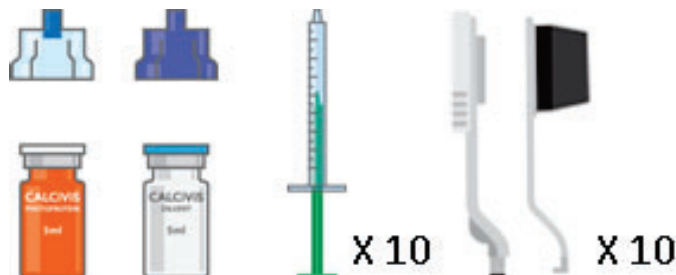
### 3 ACCESSORY AND DEVICE PREPARATION

#### 3.1 SYRINGE PREPARATION

Preparation of the CALCIVIS photoprotein and filling the syringe should be carried out as follows:

1. Wear disposable gloves
2. If CALCIVIS photoprotein has already been reconstituted proceed directly to 11.
3. Check the integrity of the packaging of all components of the CALCIVIS imaging kit: CALCIVIS single use applicator components, syringes, vial adaptors, vial of CALCIVIS photoprotein and CALCIVIS diluent.
4. Do not use if the primary packaging has been breached or wet.
5. Remove flip off tops from CALCIVIS photoprotein (white cap) and diluent vials (blue cap).
6. Remove adaptors from packaging and fit to vials of CALCIVIS photoprotein and diluent. **Whilst fitting ensure the adaptor pushes straight down and not at an angle.**  
Fit BLUE adaptor to vial of CALCIVIS diluent.  
Fit CLEAR adaptor to vial of CALCIVIS photoprotein.
7. To reconstitute CALCIVIS photoprotein with CALCIVIS diluent, screw together in vertical position ensuring the opaque (amber) vial is at the bottom.  
**Note: Ensure fluid passes from the CALCIVIS diluent vial to the CALCIVIS photoprotein vial. A small residual amount may remain in the diluent vial.**
8. Detach CALCIVIS diluent from CALCIVIS photoprotein by unscrewing (Discard empty CALCIVIS diluent bottle)
9. Gently mix by swirling. Leave to stand for 30 seconds before withdrawing fluid
10. Write date of reconstitution and expiry date on label on side of vial.
11. Wipe top of adaptor with IPA wipe and leave for 20 seconds to dry. Insert syringe into vial adaptor and withdraw 0.37ml solution from vial
12. **If required, push Syringe plunger to empty fluid back into vial to remove any air bubbles.** Carefully withdraw 0.37ml using syringe (avoiding bubbles).  
**If bubbles are present, gently tap the side of the syringe to dislodge.**
13. The CALCIVIS photoprotein syringe is now ready to be inserted into the CALCIVIS imaging device.
14. Place residual CALCIVIS photoprotein vial (in its box) in refrigerator (2-8°C).

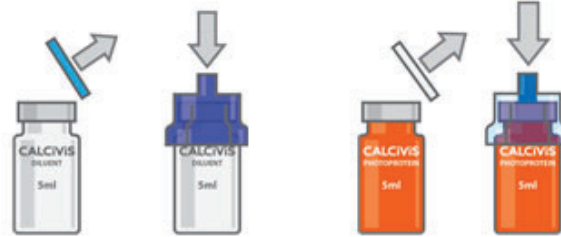
#### CALCIVIS imaging kit components



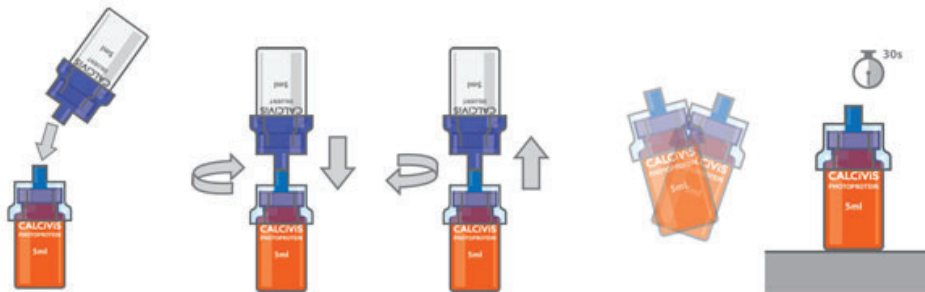
## Instructions for Preparation



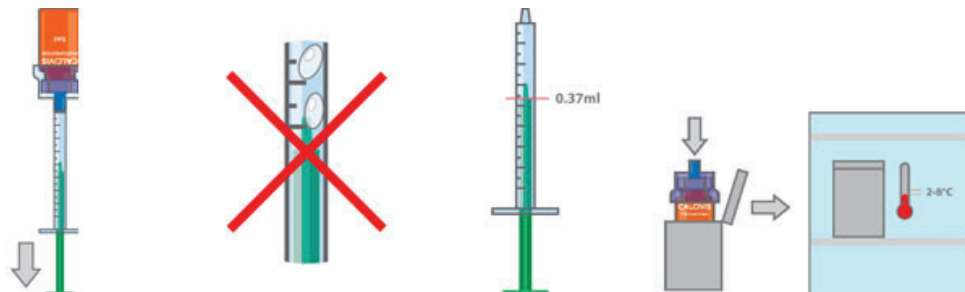
1) Wear Gloves



2) Flip off vial caps and attach adapters:  
Blue → Diluent; Clear → Photoprotein



3) Place photoprotein on flat surface and bring diluent to photoprotein.  
4) Screw the applicators together to draw the fluid through and unscrew to disconnect  
5) Mix gently and let sit for 30s



6) Connect the syringe to the adapter and with the vial upside down draw photoprotein into syringe  
7) Ensure there are no bubbles in the syringe. Move the plunger up and down to remove bubbles  
8) Fill to 0.37 ml and remove vial. Return the vial to the fridge.

## 3.2 DEVICE PREPARATION

Preparation of the CALCIVIS imaging device should be carried out as follows:

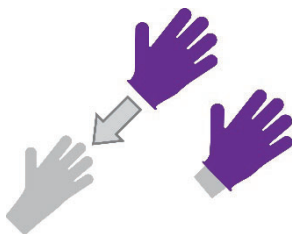
- Wear gloves
- Check CALCIVIS imaging device is clean, if not perform clean as in section 7.
- With the CALCIVIS imaging device upside down (syringe door up) in its storage cradle, remove the syringe compartment cover, on the underside of the device body.
- Insert the pre-filled syringe into the underside compartment, locating the T-bar and end of plunger into the matching slots on underside of the device.
- Re-fit the syringe compartment cover (front end first).



## 3.3 CALCIVIS APPLICATOR PREPARATION

Preparation of the CALCIVIS applicator should be carried out as follows:

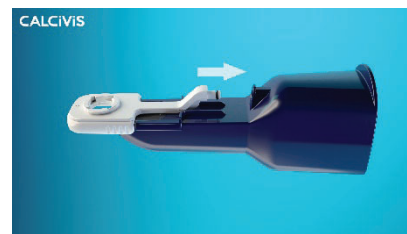
- Wear disposable gloves
- Obtain CALCIVIS applicator main body.
- Firmly push the CALCIVIS applicator main body into place over the CALCIVIS imaging device – an audible or tactile ‘click’ should be heard or felt when correctly attached.
- Remove the single use CALCIVIS applicator fluid channel from its pouch and slide into place over the CALCIVIS applicator main body
- The device is now ready for priming



Wear gloves



Fit main body to device



Fit fluid channel to Applicator main body

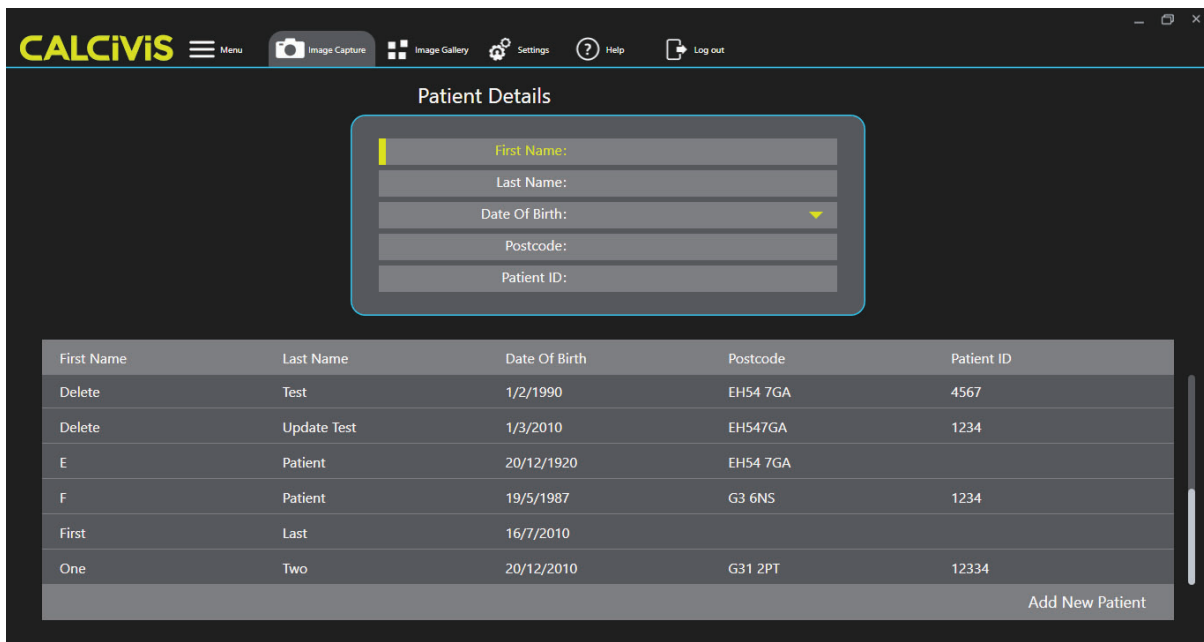
## 4 ENTERING PATIENT DETAILS USING IMAGE CAPTURE SCREENS

### 4.1 STANDALONE MODE (NOT INTEGRATED TO OTHER IMAGE MANAGEMENT SYSTEM)

In standalone mode (i.e. when not integrated to other Image Management System) the Image Capture screens allow the user to:

- Select a pre-existing patient via list of patients or search function.
- Enter a new patient's details
- Enter CALCIVIS imaging kit lot numbers
- Enter patient ID
- Prime the CALCIVIS imaging device
- On completion of successful priming, capture images

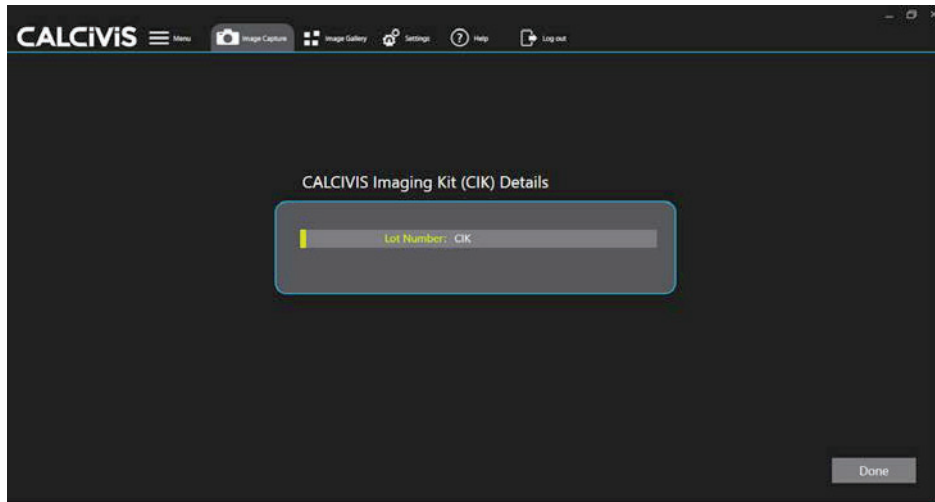
#### 4.1.1 ENTER PATIENT DETAILS



The screenshot displays the CALCIVIS software interface. At the top, there is a navigation bar with the CALCIVIS logo, a menu icon, and buttons for Image Capture, Image Gallery, Settings, Help, and Log out. The main content area is titled 'Patient Details' and features a form with the following fields: First Name, Last Name, Date Of Birth (with a dropdown arrow), Postcode, and Patient ID. Below the form is a table listing existing patients with columns for First Name, Last Name, Date Of Birth, Postcode, and Patient ID. An 'Add New Patient' button is located at the bottom right of the table area.

First Name	Last Name	Date Of Birth	Postcode	Patient ID
Delete	Test	1/2/1990	EH54 7GA	4567
Delete	Update Test	1/3/2010	EH547GA	1234
E	Patient	20/12/1920	EH54 7GA	
F	Patient	19/5/1987	G3 6NS	1234
First	Last	16/7/2010		
One	Two	20/12/2010	G31 2PT	12334

## 4.1.2 CALCIVIS IMAGING KIT DETAILS



CALCIVIS Imaging Kit (CIK) Details

Lot Number: CIK

Done

Enter CALCIVIS imaging kit lot number found on kit packaging (if required by administrator settings).

## 4.2 INTEGRATED MODE (INTEGRATED TO SOFTWARE OF EXCELLENCE IMAGE MANAGEMENT SYSTEM)

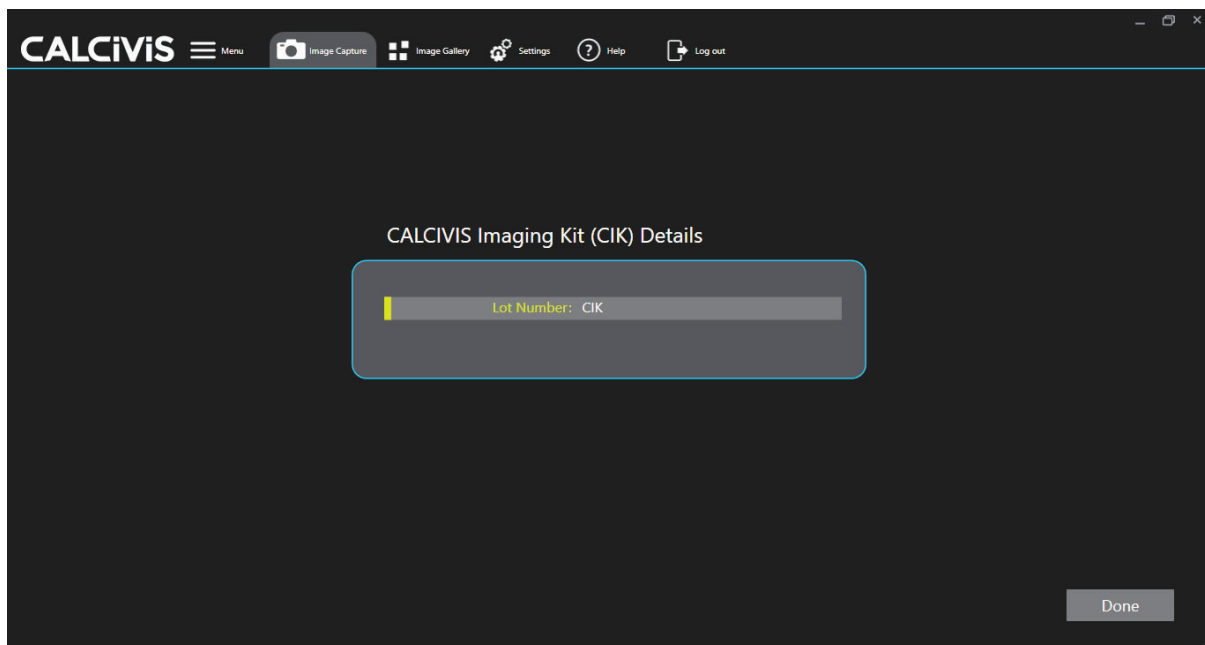
In Integrated mode (i.e. when integrated to other Image Management System [IMS]) the Image Capture screens allow the user to:

- Enter CALCIVIS imaging kit lot numbers
- Prime the CALCIVIS imaging device
- On completion of successful priming, capture images

### 4.2.1 PATIENT DETAILS

Patient details that have been selected in the IMS will follow through to the CALCIVIS software, therefore it is not necessary to re-enter patient details.

### 4.2.2 CALCIVIS IMAGING KIT DETAILS



Enter CALCIVIS imaging kit lot number found on kit packaging (if required by administrator settings).



### 4.3 PRIMING THE CALCIVIS IMAGING DEVICE

After loading syringe containing reconstituted CALCIVIS photoprotein and fitting main body of the applicator along with the single use fluid channel of the applicator, confirm the operation has been completed by clicking 'DONE'

Prime the CALCIVIS imaging device by pressing the actuator Button.

**CAUTION: the CALCIVIS imaging device will dispense some fluid while priming. Ensure it is held over tissue paper to visually confirm fluid is dispensed.**

**Ensure fluid is dispensed before moving to next stage. If fluid is not dispensed it indicated something is wrong with the set up. Remove the applicator and syringe and replace with new CALCIVIS photoprotein filled syringe and CALCIVIS applicator.**

If any doubt over the priming or overall set up a function check test may be performed as detailed in the Troubleshooting Section;

On completion of successful priming insert the CALCIVIS applicator light shield and clip into place



## **5 IMAGING OF TEETH**

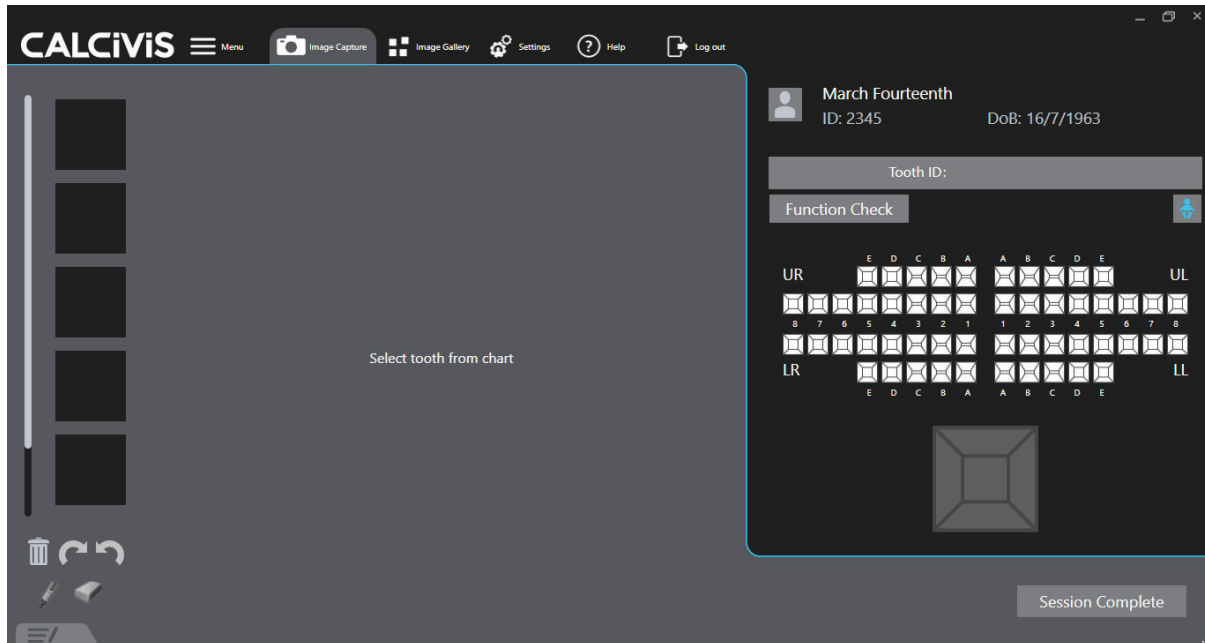
### **5.1 PREPARATION OF TEETH**

Once a tooth surface of interest has been identified and selected for assessment with the CALCIVIS imaging system, the following procedure should be followed:

- Use a blunt / ball ended probe to remove gross accumulations of debris and dental plaque from the tooth surface if required
- For each tooth surface to be imaged brush the entire exposed tooth surface with a toothbrush and water (dental paste may be used if required and followed by brushing with water)
- Thoroughly rinse the tooth surface with a 3-in-1 (water only, then air-water spray). The patient should be asked to spit out residual water after the 3-in-1 rinse.
- As saliva contains calcium ions any gross contamination of the tooth surface under investigation, may interfere with the results. Where possible isolate the tooth from saliva with the use of isolation items such as mini-dams, cotton rolls, dry tips, saliva ejectors etc.
- Dry the tooth with compressed air.

## 5.2 TOOTH IMAGING PROCESS

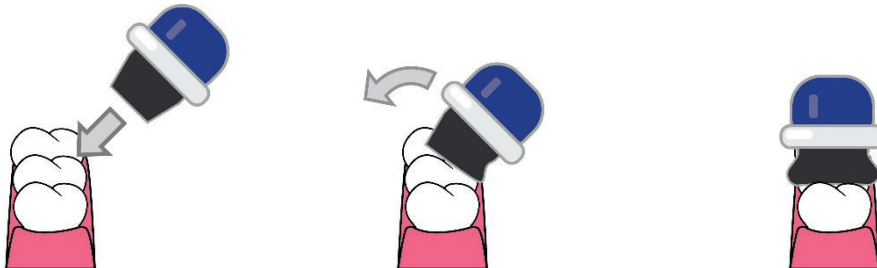
On completion of priming the CALCIVIS imaging system is ready for imaging.



Click on the tooth ID chart to identify which tooth is to be imaged, followed by surface to be imaged.

**Note: Ensure the tooth surface to be imaged is clean, rinsed and thoroughly air-dried before imaging. Air-dry the tooth for approximately 5 - 10 seconds immediately prior to imaging.**

Position the tip of the applicator over the tooth surface of interest. Ensure the surface is in focus and ambient light has been eliminated. Envelop the chosen accessible surface of interest by approaching from the lingual side of the tooth at an angle of about 45 degrees and working the light shield over the tooth surface until the chosen accessible surface is completely covered then press firmly to get correct focus.



A live video stream can be viewed on the screen to ensure correct positioning over the tooth surface of interest. When ready capture an image of the tooth surface of interest.

**Note: Imaging takes approximately 1 second and it is important to ensure the CALCIVIS imaging device is held still during imaging to avoid blurred images due to camera shake. In addition, for best results avoid direct illumination of the mouth during the actual imaging process by ensuring the main overhead illumination lights are switched off.**

To trigger the start of the sequence, press the Sequence Activation Button on the CALCIVIS imaging device

**Note: An audible ‘whirl’ indicates that the system is about to apply CALCIVIS photoprotein and image. Ensure the CALCIVIS imaging device is correctly positioned and held still until imaging has finished and the image displayed on screen.**

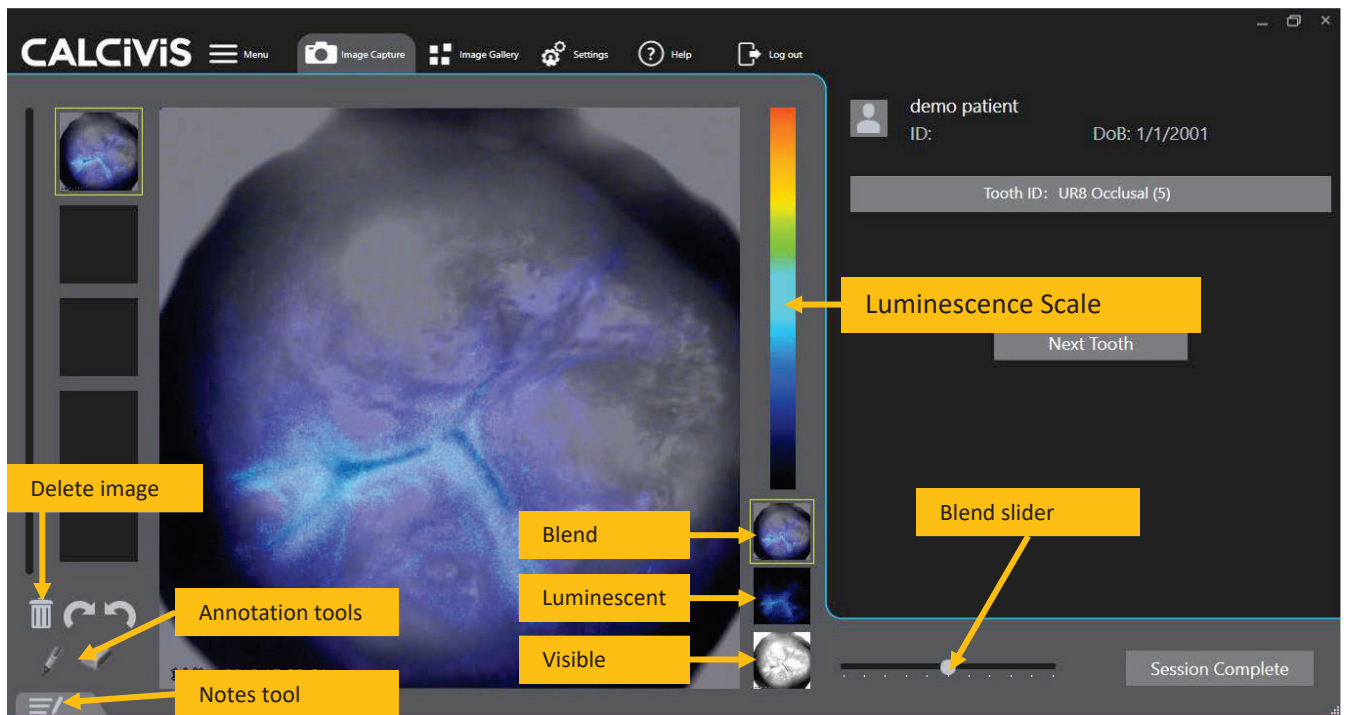
### 5.3 ADDITIONAL INFORMATION ON IMAGING

- When imaging multiple teeth in one sitting ensure all lower teeth are imaged first.
- Having previously cleaned all teeth to be assessed (as detailed above in 5.1), **air-dry the tooth for approximately 5 - 10 seconds immediately prior to imaging.**
- **As the CALCIVIS imaging device is detecting very faint transient luminescence from teeth, for best results the device should be used in a low light setting. Avoid sources of direct light into patients' mouth, ensuring the main overhead illumination lighting is switched off.**
- **When imaging upper teeth ensure the patient is in the fully reclined position.**
- To ensure best surface coverage, wherever possible, place the CALCIVIS applicator black tip fully over the tooth to be assessed. This will ensure optimal focus, best tooth surface coverage of CALCIVIS photoprotein and exclusion of ambient light that could spoil the image.
- Do not attempt to image teeth if the tooth cannot be accessed without causing trauma or upset to the patient.
- Using the video stream on the laptop or surgery monitor carefully centre the display directly over the area of interest (e.g. white spot lesion). To initiate imaging press actuator button on upper side of the CALCIVIS imaging device.
- Hold the CALCIVIS imaging device steady for approximately 1 second until imaging is complete.
- Remove CALCIVIS imaging device from patient's mouth and ask patient to rinse any residual photoprotein solution from their mouth.
- Repeat as necessary for other teeth, beginning with the air-drying procedure, **up to a maximum of 5 teeth.**
- **If greater than 5 teeth (up to a maximum of 20 per sitting) are to be imaged a new syringe will need to be fitted.**

#### IMAGE COUNT

The software will allow a maximum of 5 applications per session. If additional images are required end current session and the device should be dismantled and cleaned according to section 7. A new syringe of CALCIVIS photoprotein can be inserted and the same applicator used if for the same patient.

## 6 IMAGE REVIEW (AVAILABLE FOR BOTH INTEGRATED AND STANDALONE MODES)



On capturing an image the live camera feed will stop and the captured image will be displayed in the image review screen.

The Review screen allows the user to toggle between:

- Visible light images
- Luminescent images
- Blended images

The user is able to:

- Adjust the blending level of the visible and luminescence images
- Rotate images
- Delete the image (the image can be deleted if unsuitable, otherwise it will automatically be saved when the session is complete).
- Visualise the level of luminescence on the scale by left clicking on the mouse when hovering over an area of interest
- Annotate the image using the annotation tools

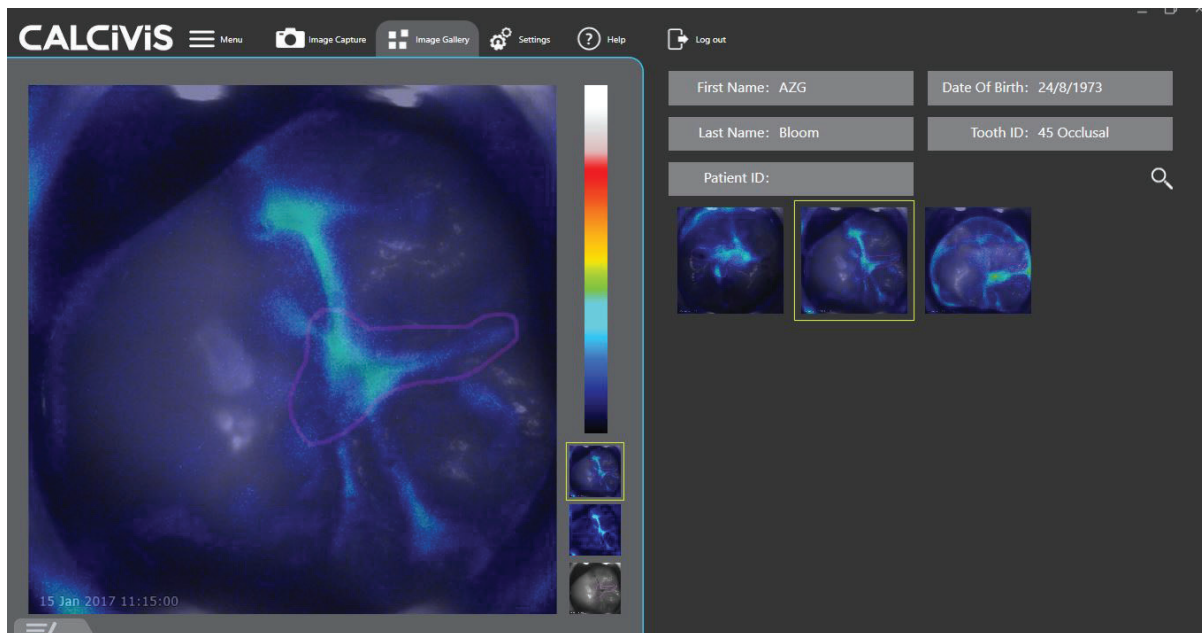
- Add notes to the image using the notes tool

When all images have been taken click on session complete. This will save the images from the session.

**IMPORTANT:** If session complete is not clicked images will not be saved.

**IMPORTANT:** Images will be saved at the blend level set (a warning will be provided if out with 25 – 75% blend)

## 6.1 THE IMAGE GALLERY (ONLY AVAILABLE IN “STANDALONE” VERSION. NOT AVAILABLE WHEN INTEGRATED TO PRACTICE IMAGE MANAGEMENT SOFTWARE).



The Image Gallery allows the user to:

- Search previously captured images using patient details
- Select multiple images to view side by side and compare
- Review
  - Visible light images
  - Luminescent images

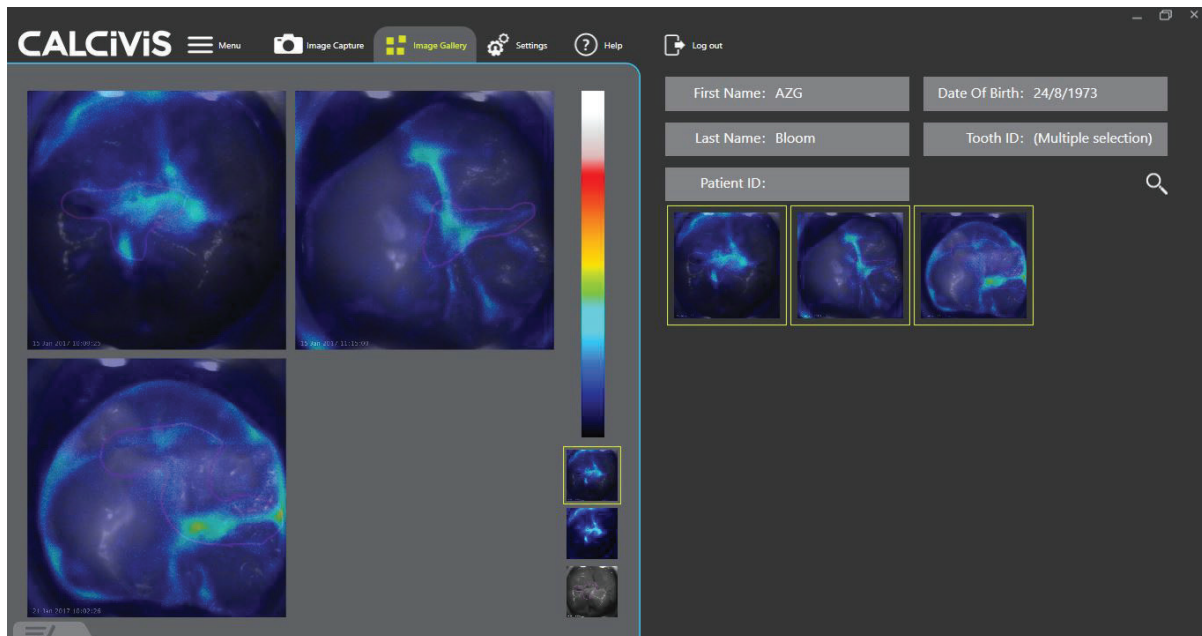


- Blended images

The user is able to:

- Toggle between blended, visible and luminescence images in the main window
- Add notes to the images using the notes tool
- Search by clicking the search symbol (magnifying glass) and entering patient details
- Select patient from drop down menu
- Select image from drop down menu
- Confirm patient details using 'details tab'
- View images using 'image tab'

Multiple images can be displayed side by side on the main screen for comparison.



## 6.2 IMAGE INTERPRETATION AND ANALYSIS

Image interpretation and analysis should only be performed by trained professionals. Areas of luminescence represent areas of greatest concentration of free calcium, which is indicative of on-going demineralisation.

Very high levels of apparent luminescence in unexpected areas may be due to ambient light leak. If this is seen repeat imaging ensuring all **main overhead illumination** lights are off and no external light source is entering the mouth during imaging.

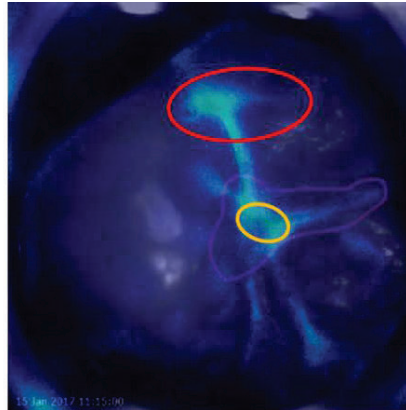
Very high levels of apparent luminescence in unexpected areas may also be due to gross contamination with saliva. If this is seen repeat imaging ensuring tooth surface is **thoroughly rinsed and dried**.

### 6.2.1 TYPICAL IMAGES SEEN WITH THE CALCIVIS IMAGING SYSTEM

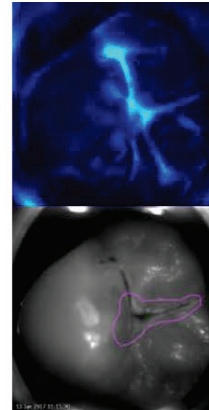
#### Active Demineralisation



Central fossa white spot (circled in orange) in fissure entrance (noted at visual examination) along with distal (upper) white spot areas (circled in red) indicative of more intense demineralisation (not highlighted as the specific area of interest in initial visual examination (see purple drawing in next image).

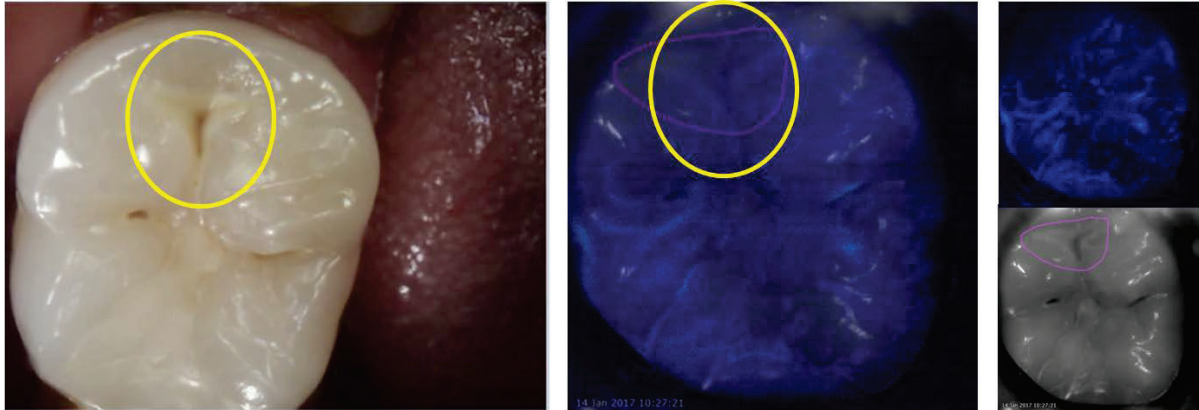


CALCIVIS blended image clearly shows areas of luminescence in central fissure entrance and upper white spot region, indicative of active demineralisation in both these areas.



CALCIVIS raw images

Arrested lesion

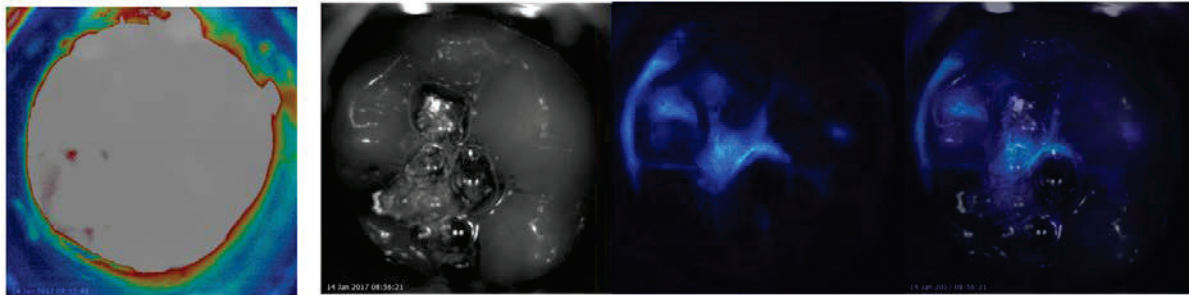


Area around caries yellow/brown indicative of arresting lesion.

CALCIVIS blended image shows no luminescence in this area

CALCIVIS raw images

6.2.2 EXAMPLE IMAGES OF POTENTIAL CONFOUNDING ISSUES



Ambient Light ingress

Gross saliva contamination evidenced by bubbles in visible image

If these sort of images are seen or there is any doubt over the images a repeat should be taken ensuring the tooth surface is clean and dry and sources of external light have been eliminated.

## 7 DISMANTLING, CLEANING AND DISPOSAL INSTRUCTIONS

After each patient use, the CALCIVIS imaging device should be disconnected from the USB 3 port and dismantled and cleaned according to the following protocol:

- Detach CALCIVIS imaging device cable from USB 3 port.
- Remove gloves and de-contaminate hands.
- Use fresh pair of gloves.
- Remove the applicator by twisting to unclip the light shield, depressing the latch button and pulling off the Applicator. The applicator should easily detach. If difficult to remove the thumb guard can be used to apply additional leverage.



- Dispose of Applicator to clinical waste.
- Open lower case of CALCIVIS imaging device and remove syringe.
- Dispose in clinical waste container
- Wipe all surfaces of the CALCIVIS imaging device thoroughly, including the housing and the inside and out of lower case cover with hospital grade disinfectant wipes, taking care to wipe all moulded parts.

## **8 MAINTENANCE, REPAIR AND DISPOSAL**

The CALCIVIS imaging device does not contain any user serviceable parts. Servicing and maintenance should only be carried out by qualified personnel. In the event of any failure, damage or malfunction the device should be returned to:

CALCIVIS Ltd.

Nine Edinburgh BioQuarter

9 Little France Road

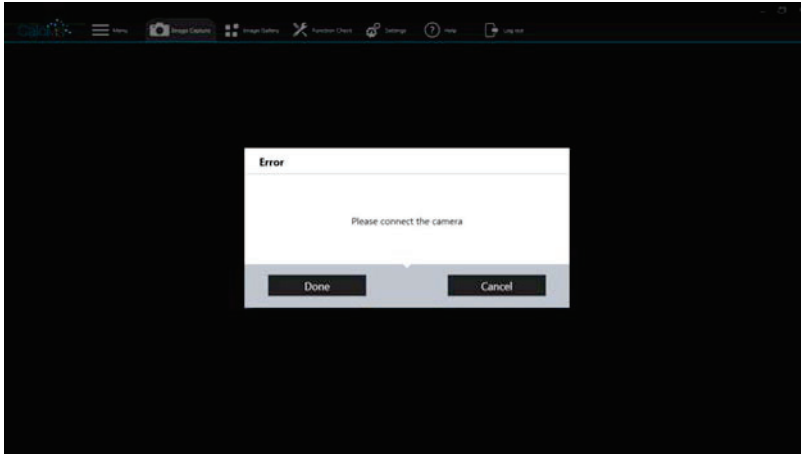
Edinburgh

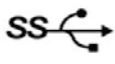
EH16 4UX

Tel: +44 131 658 5152

## 9 TROUBLESHOOTING

### 9.1 NO CAMERA FOUND ERROR MESSAGE



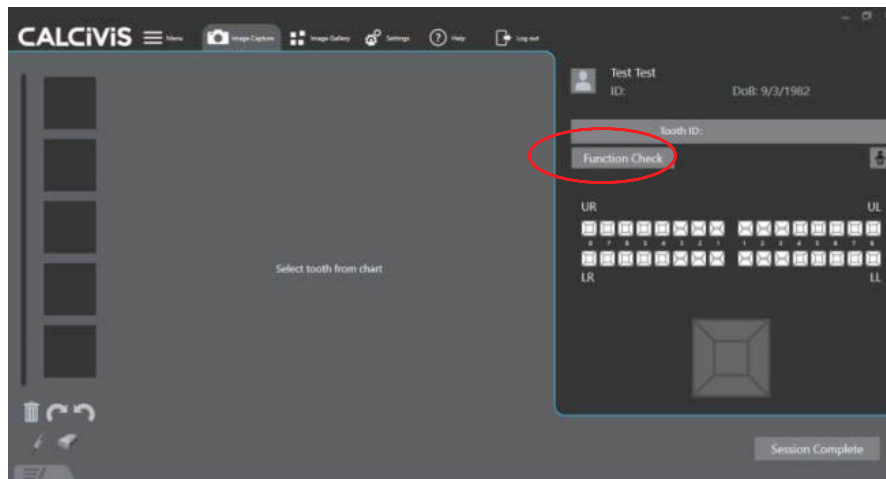
1. Exit software
2. Unplug camera from USB 3 port. Check the port is USB 3 (USB 3 ports are identified by this symbol  and/or blue connection in port)
3. Check all connections from instrument
4. Power up camera by reactivating via the USB3 port.
5. Wait at least 15 seconds (to allow camera driver to start-up)
6. Re-start software

## 9.2 FUNCTION CHECK

The Function check kit consists of a plastic tray with thermoformed wells containing a deposit of calcium chloride, which is used in conjunction with the CALCIVIS Imaging System to detect free calcium ions within the well. A positive result for the test confirms to the user that the system is functioning as intended.

The Function check kit should be used at any time the operator has doubts about the CALCIVIS imaging system set up or function.

Select the **Function Check** tool on the Image Capture Screen.



While wearing gloves, remove the cardboard sleeve and carefully remove the foil cover from one of the test wells.





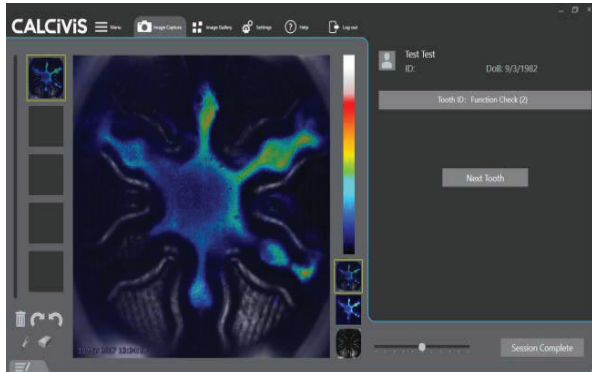
Firmly place the applicator tip into the test well.

**NOTE: The function check is to be performed without the CALCIVIS applicator light shield in place.**

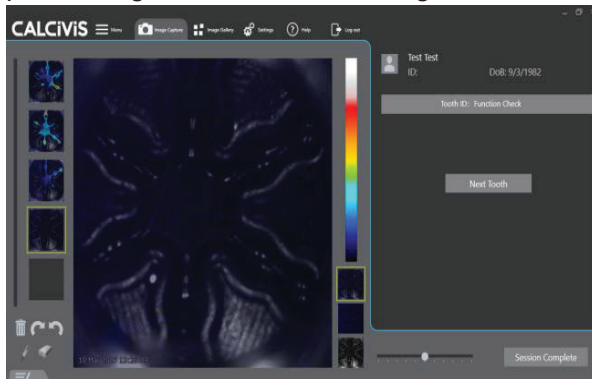


Press the **activation button** on the device.

If the function check has passes a luminescent image similar to the one below is displayed.



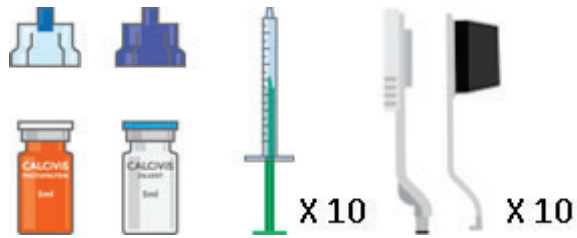
If **no** luminescence is observed, or a blank image is displayed (below), this indicates something is wrong with the set up. Click session complete, re-load with fresh Photoprotein solution before performing the function check again.



**10 NOTES**

# Calcivis Imaging Kit Instructions For Use

## CALCIVIS imaging kit components



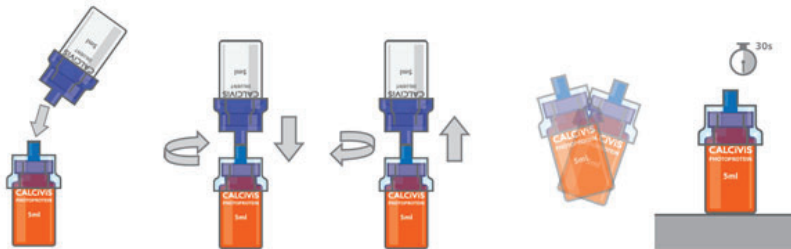
## Instructions for Preparation



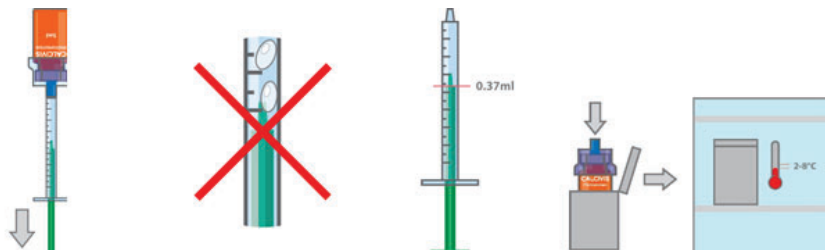
1) Wear Gloves



2) Flip off vial caps and attach adapters:  
Blue → Diluent; Clear → Photoprotein



3) Place photoprotein on flat surface and bring diluent to photoprotein.  
4) Screw the applicators together to draw the fluid through and unscrew to disconnect  
5) Mix gently and let sit for 30s



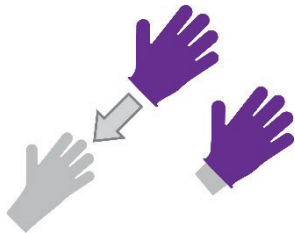
6) Connect the syringe to the adapter and with the vial upside down draw photoprotein into syringe  
7) Ensure there are no bubbles in the syringe. Move the plunger up and down to remove bubbles  
8) Fill to 0.37 ml and remove vial. Return the vial to the fridge.

For full instructions refer to User manual supplied with CALCIVIS imaging device.

## CALCIVIS APPLICATOR PREPARATION

Preparation of the CALCIVIS applicator should be carried out as follows:

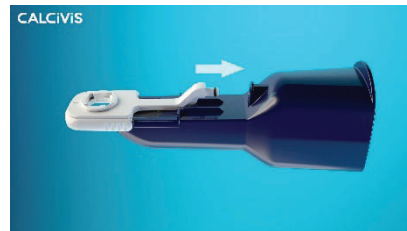
- Wear disposable gloves
- Obtain CALCIVIS applicator main body (dark blue).
- Firmly push the CALCIVIS applicator main body into place over the CALCIVIS imaging device – an audible or tactile 'click' should be heard or felt when correctly attached.
- Remove the single use CALCIVIS applicator fluid channel from its pouch and slide into place over the CALCIVIS applicator main body
- The device is now ready for priming



Wear gloves



Fit main body to device



Fit fluid channel to Applicator main body

- On completion of successful priming insert the CALCIVIS applicator light shield into the bayonet fitting and twist to clip into place



Insert the CALCIVIS applicator light shield into bayonet fitting and twist to clip into place

After use dismantle the CALCIVIS applicator by unclipping light shield and sliding the whole applicator off the device. Disposing of them safely to clinical waste.

**IMPORTANT: DO NOT REUSE THE CALCIVIS APPLICATOR COMPONENTS**

## **Function Check Kit**

The Function check kit consists of a plastic tray with thermoformed wells containing a deposit of calcium chloride, which is used in conjunction with the CALCIVIS imaging system to detect free calcium ions within the well. A positive result for the test confirms to the user that the system is functioning as intended.

The Function check kit should be used at any time the operator has doubts about the CALCIVIS imaging system set up or function.

**It is important to note that the CALCIVIS imaging system is non-quantitative therefore the function check is a gross check that the system has been correctly set up, that correct quality CALCIVIS photoprotein is dispensed and a luminescent image captured, it is not for calibration purposes.**

For full instructions refer to User Manual supplied with the CALCIVIS imaging device.