# CUBACLINICAL

Incorporating

## CUBA *plus+* software v4

# USER MANUAL

## - PLEASE READ THIS MANUAL THOROUGHLY -

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# 1.0 Introduction and Background

The CUBAClinical is a patented 'dry' Ultrasonic Bone Sonometry System. By placing the calcaneus (heel bone) between two directly contacting Ultrasonic Transducers, rapid measurements of Broadband Ultrasonic Attenuation (BUA) are obtained. The calcaneus is a bone site of proven sensitivity to osteoporotic change.

This chapter provides an overview about ultrasound bone sonometry and the CUBAClinical. It includes a discussion of ultrasound measurement, safety precautions, system components and product specifications.

**Essential prescribing information**

***Caution: Federal (U.S.A.) Law restricts this device to sale by or on the order of a physician.***

## 1.1 Device Description

The CUBAClinical consists of the measurement unit, its power cord and computer connection cord, foot positioning inserts, and accessories. See section 'What is Supplied', below, for a complete list of accessories.

The CUBAClinical takes an ultrasound measurement through the patient's heel. The patient is seated with the foot accurately positioned into the footwell, using the correct positioning insert. The foot and lower part of the leg are secured using two Velcro® straps. Ultrasound gel is applied to the face of the silicone pads and to the sides of the heel to provide acoustic coupling. The silicone pads are brought into contact with each side of the patient's heel by means of a motorized mechanism. Inaudible sound waves are transmitted from one of the transducers through the heel and received by the other transducer. Quantitative parameters describing the attenuation in the heel are measured.

Patient examination time is short, with a typical measurement time of 1 minute (including a settling period).

## 1.2 Intended Use / Indications

The intended use of the CUBAClinical Ultrasonic Bone Sonometer is to perform a quantitative ultrasound measurement of the calcaneus (heel bone), the results of which can be used in conjunction with other clinical risk factors as an aid for the diagnosis of osteoporosis and other medical conditions leading to reduced bone density and ultimately in the determination of fracture risk.

The CUBAClinical measures two parameters, Broadband Ultrasound Attenuation (BUA in dB/MHz) which is used for the clinical measurement and Velocity of Sound (VOS, in m/s) which is used for QA purposes only. The BUA output is expressed both as an absolute value

and, with reference to the embedded Normative Data, as a T-Score, a Z-Score, and the percent expected (age-matched).

## 1.3 Contraindications

There are no contraindications.

## 1.4 Warnings

The CUBAClinical should not be used on subjects with breached skin (abraded skin) or open sores in any area of the lower leg, ankle, or foot that comes in contact with the System. Doing so may increase the risk of transmission of infection between patients.

The CUBAClinical requires proper cleaning and disinfecting procedures between each patient use. Doing so can help prevent transmission of infection between patients. Refer to Section 2.5 for cleaning and disinfection instructions.

Verify that the operating voltage specified on the rear panel of the System states 100 - 120 V AC, 50 - 60 Hz.

Any electrical outlet to which the CUBAClinical is connected **MUST** incorporate an effective earth (GROUND) connection.

Never use a damaged mains cable or allow loose connecting wires.

The CUBAClinical System is <u>not</u> designed for use in explosive or oxygen-enriched atmospheres.

All maintenance on the equipment must be performed by suitably qualified and trained personnel.

It is important for all users of the CUBAClinical to note and act upon all precautions and warnings in this and any other document concerned with this equipment particularly with reference to the following :

- The equipment must only be connected to the correct mains supply
- US models: are supplied with a "Hospital Grade" mains supply cord set meeting specification UL498. This type of cord set must be used. Grounding reliability can only be achieved when the equipment is connected, using the aforementioned cord set, to a receptacle labeled "Hospital Grade".
- After applying ultrasound gel to the patient and transducers, users should clean the gel from their hands before touching the equipment or computer.
- Hazardous voltages are present within the unit. The mains supply must be isolated before any maintenance work is performed or the enclosure removed.
- The use of components, modules or any modifications not approved by McCue will invalidate the warranty on the product.

The CUBAClinical is **NOT designed to be USER serviceable**. Other than for external cleaning, no regular maintenance is required.

Removal of the outer case and any unauthorized adjustment to the electronics within will result in the need for the System to be recalibrated by an authorized service agent.

Contact your authorized service agent for repairs. Unauthorized repairs or modifications will VOID all warranties.

## 1.5 Precautions

- The CUBAClinical is not protected against the ingress of liquids and should be used only in a clean, dry environment.
- Do not store the CUBAClinical near to a heat source, window or air conditioner.
- Only the CUBAClinical QA Phantom should be used to verify the calibration of the CUBAClinical System.
- The QA Phantom should be stored close to the CUBAClinical and under the same conditions.
- Never leave the QA Phantom in the CUBAClinical footwell with the transducers in the closed position.
- CUBAClinical ultrasound gel is for external use only.
- Interfacing equipment (Computer, printer) used with the CUBAClinical must meet IEC 950, or equivalent safety standards.
- Animal studies of the material used for the CUBAClinical case and external parts (acrylic-coated ABS plastic) suggest that this material may be a potential sensitizer.

## 1.6 Adverse Events

There are no known potentially adverse effects from the CUBAClinical on health. Since the launch of the CUBAClinical in June 1992 over 500 Systems have been sold world-wide (except North America) and many tens of thousands of measurements have been performed. No adverse events of any kind have been reported.

## 1.7 Clinical Studies

Five studies performed at six sites in the United States and Europe were conducted to assess the safety, effectiveness, and clinical utility of the McCue CUBAClinical. Study A evaluated the CUBAClinical and four other calcaneal bone assessment instruments for precision, correlation, and discrimination ability. Study B was conducted to determine the possible contribution of CUBAClinical BUA for assessing risk of osteoporotic fracture in the elderly. Results for Studies A and B are described here. Results of three additional studies conducted at two sites in the United Kingdom which demonstrate the diagnostic performance of the CUBAClinical and how it compares with DEXA BMD are provided in Appendix 1 to this Manual.

## STUDY A: Fosamax Protocol 349

This study was conducted at two clinical sites in the United States to determine if measuring skeletal status at the calcaneus is a useful technique for diagnosis of osteoporosis and evaluated the CUBAClinical and four other calcaneal bone assessment instruments for precision, correlation, and discrimination ability. The study enrolled a total of 161 Caucasian women: 53 were "young normal" women between the ages of 20 and 35 (mean age: 30.2); and 52 were osteoporotic women with no history of fracture; and 56 were osteoporotic women without a history of fracture. The 108 osteoporotic women were all between the age of 55 and 92 (mean age: 72.5). Subjects were considered to be osteoporotic if they had a femoral neck or trochanter BMD T-score of -2.5 or lower. CUBAClinical BUA measurements were performed on the subjects using the CUBAClinical as well as DEXA and SEXA of the calcaneus, hip, and spine. In addition, measurements were performed using three other calcaneal ultrasound devices, but these devices were not included in the analysis presented in the PMA. Complete results for all devices tested are provided in a report published by Greenspan, et al (1997).

Femoral neck and trochanter BMD T-Scores using device-specific reference populations were used to qualify subjects for enrollment in the osteoporotic cohorts. T-Scores for all instruments for all other analyses were determined using the young normal subjects, thereby providing a common reference population.

Pearson's product moment correlation coefficients were determined for age and CUBAClinical BUA measurements and for the DEXA and SEXA devices. For all study subjects, the correlation between subject age and the instrument measurements ranged from -0.677 (BMD calcaneus) to -0.836 (BMD femoral neck). The correlation coefficient for CUBAClinical BUA was approximately in the middle of this range at -0.743.

The correlation of the CUBAClinical BUA T-scores to the T-scores for the BMD measurements were determined. Pearson's correlation coefficients for BUA versus each of the DEXA and SEXA devices ranged from 0.696 (BUA versus DEXA of the trochanter) to 0.821 (BUA versus DEXA of the calcaneus). Correlations among the different BMD measurements ranged from 0.729 (DEXA calcaneus versus DEXA femoral neck) to 0.908 (DEXA calcaneus versus SEXA calcaneus).

T-scores for fracture and non-fracture cohorts are given in Table 1 for CUBAClinical BUA measurements, DEXA measurements, and SEXA measurements at different anatomical sites. For all of the devices studied, the mean T-scores for the fracture groups were significantly lower than the mean T-scores for the non-fracture groups ($p<.02$). Duncan's Multiple Range Test was used to compare the mean T-scores for the CUBAClinical BUA and the SEXA and DEXA measurements for all osteoporotic subjects. This test found that the mean T-score for CUBAClinical BUA was not significantly different from the mean BMD T-scores for DEXA calcaneus and DEXA trochanter. BMD T-scores for DEXA femoral neck and SEXA calcaneus were also not significantly different.



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Table 1. Summary of T-Scores for Study A Osteoporotic Subjects

| Instrument | | Osteoporotic | | |
|---|---|---|---|---|
| | | No Fracture (n=49) | Fracture (n=55) | All (n=104) |
| CUBAClinical BUA | Mean | -1.77 | -2.24 | -2.02 |
| | SD | 0.837 | 0.859 | 0.877 |
| OsteoAnalyzer (BMC) | Mean | -1.99 | -2.62 | -2.32 |
| (SEXA calcaneus) | SD | 1.015 | 1.186 | 1.148 |
| QDR-1500/2000 (BMD) | Mean | -1.76 | -2.305 | -2.05 |
| (DEXA calcaneus) | SD | 1.141 | 1.219 | 1.208 |
| QDR-1500/2000 (BMD) | Mean | -1.71 | -2.13 | -1.93 |
| (DEXA trochanter) | SD | 0.698 | 0.810 | 0.783 |
| QDR-1500/2000 (BMD) | Mean | -2.30 | -2.54 | -2.43 |
| (DEXA femoral neck) | SD | 0.413 | 0.592 | 0.527 |

The ability of CUBAClinical BUA, DEXA calcaneus BMD, and SEXA calcaneus BMD to discriminate between osteoporotic and non-osteoporotic controls was assessed for T-score thresholds of -2.5 and -2.0. For a T-score threshold of -2.5, the proportion of subjects classified as osteoporotic by CUBAClinical BUA was 31 percent. This compares to 39 percent and 47 percent for DEXA calcaneus and SEXA calcaneus, respectively. For a T-score threshold of -2.0, the number of subjects correctly classified as osteoporotic ranged from 53 to 69 percent, with CUBAClinical BUA at 58 percent.

Receiver-Operator Characteristic (ROC) curves were generated to determine the ability of CUBAClinical BUA and DEXA and SEXA of the calcaneus to discriminate osteoporotic subjects from the young normal control group. In addition, ROCs and the areas under the ROC curves were generated to discriminate between osteoporotic subjects with fractures from those without fractures. The area under an ROC curve provides a figure of merit for comparing one curve to another. The AUC must be greater than 0.5 if the diagnostic ability is better than chance. A summary of the AUCs obtained for the three instruments is provided in Table 2.

Table 2. Areas Under the ROC Curves for Study A

| Instrument | Control vs Osteoporotic AUC (95%CI) | Osteoporotic w/o vs Osteoporotic w/fracture AUC (95%CI) |
|---|---|---|
| CUBAClinical BUA | 0.93 (0.89, 0.97) | 0.63 (0.53, 0.73) |
| OsteoAnalyzer (SEXA calcaneus) | 0.93 (0.89, 0.97) | 0.65 (0.55, 0.75) |
| QDR 1500/2000 (DEXA calcaneus) | 0.90 (0.86, 0.94) | 0.62 (0.52, 0.72) |
| QDR 1500/2000 (DEXA trochanter) | 0.93 (0.89, 0.97) | 0.65 (0.52, 0.75) |
| QDR 1500/2000 (DEXA femoral neck) | 0.98 (0.96, 1.00) | 0.60 (0.48, 0.72) |

To further compare the discriminatory ability of CUBAClinical BUA to the X-ray absorptiometry instruments, the sensitivity and specificity of each instrument was determined for T-score thresholds of -1.5, -2.0, and -2.5. The results, summarized in Table 3, indicate that the sensitivity and specificity of CUBAClinical BUA is comparable to that of SEXA of the calcaneus and DEXA of the calcaneus.

Table 3. Comparison of Sensitivity and Specificity of Calcaneal Instruments in Study A

| Instrument | T-Score Threshold | Sensitivity (%) | Specificity (%) |
|---|---|---|---|
| CUBAClinical BUA | -1.5 | 77 | 96 |
| | -2.0 | 58 | 96 |
| | -2.5 | 31 | 100 |
| QDR-1500/2000 (DEXA calcaneus) | -1.5 | 69 | 92 |
| | -2.0 | 54 | 98 |
| | -2.5 | 36 | 98 |
| OsteoAnalyzer (SEXA calcaneus) | -1.5 | 77 | 94 |
| | -2.0 | 67 | 96 |
| | -2.5 | 44 | 100 |

## STUDY B: Netherlands Study of Fracture Risk

This prospective longitudinal study was conducted to determine the possible contribution of CUBAClinical BUA for assessing risk of osteoporotic fracture in the elderly. The study was conducted at the Institute of Research in Extramural Medicine, Academic Hospital, Vrije University, Amsterdam, The Netherlands. Dr. S.M.F. Pluijm was the Principle Investigator. A total of 710 Caucasian subjects between the ages of 70 and 99 were enrolled in the study, of whom 578 were women and 132 were men. Subjects were excluded if they were unable to give informed consent, had a history of calcaneal fracture, were confined to bed, or used a wheelchair.

CUBAClinical measurements were performed at time of enrollment. Subjects were contacted every six months by telephone or self-administered mail questionnaire to determine if they had a fall or fracture during the previous month. Fractures were verified with the subject's primary physician. During the time of the study, 168 subjects died and 5 were lost to follow-up. The study accumulated 1844 person-years of follow-up (median: 2.8 years, maximum: 3.7 years).

During the period of follow-up, 77 of the subjects (73 females and 4 males) sustained a total of 96 fractures (31 hip and 65 other non-spinal fractures). Table 4 compares the baseline CUBAClinical BUA measurement for the 77 subjects with fractures and the subjects without fractures. The differences in BUA between the fracture and non-fracture groups were statistically significant for both men and women.

Table 4. Summary of Baseline CUBAClinical BUA Measurements by Fracture Status and Sex for Study B

| | CUBAClinical BUA (dB/MHz) (Mean (SD)) | | |
|---|---|---|---|
| | Fracture | Non Fracture | p value* |
| Female<br>Mean (SD) | n=73<br>51.27 (15.88) | n=503<br>56.92 (17.52) | 0.010 |
| Male<br>Mean (SD) | n=4<br>66.81 (16.56) | n=128<br>81.05 (21.57) | 0.194 |
| Combined<br>Mean (SD) | n=77<br>52.08 (16.18) | n=631<br>61.81 (20.80) | <0.001 |

*Significance level for paired t-test comparing mean for fracture versus non-fracture subjects.*

Relative hazard ratios were determined using Cox proportional hazard regression and are reported here with 95 percent confidence intervals. The relative hazard ratio of hip fracture, other non-spinal fracture, and any non-spinal fracture for one standard deviation decrease in CUBAClinical BUA is summarized by subject sex and for all subjects in Table 5. An increased relative hazard ratio is indicated by a relative risk of greater than 1.0. As shown in Table 5, the relative hazard ratio for CUBAClinical BUA is greater than 1.0 for hip fractures and any fracture in female subjects. The lower 95 percent confidence interval is less than 1.0 for other non-spinal fractures, and for all fracture endpoints in the male population.

Table 5. Relative Risk of Hip, Other Non-Spinal, and Any Non-Spinal Fracture for CUBAClinical BUA for Study B

| Gender | | Hip Fracture | | Other Non-Spinal Fractures | | Any Non-Spinal Fracture | |
|---|---|---|---|---|---|---|---|
| | | RR | 95%CI | RR | 95%CI | RR | 95%CI |
| Females | BUA | 2.27 | 1.41-3.66 | 1.29 | 0.96 - 1.73 | 1.52 | 1.17 - 1.97 |
| Males | BUA | 2.68 | 0.79 - 9.06 | 2.71 | 0.24 - 30.71 | 2.68 | 0.79 - 9.06 |
| Overall | BUA | 2.34 | 1.46 - 3.75 | 1.62 | 1.18 - 2.22 | 1.83 | 1.39 - 2.42 |

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## 1.8 Individualization of treatment

The CUBAClinical measures BUA of the heel. These results are used by the physician to assess skeletal status in the evaluation of patients at risk of osteoporosis and other metabolic bone conditions and / or patients who may have reduced bone density due to medical conditions indirectly affecting bone mineral metabolism, medications prescribed for other conditions, heritable or genetic factors, lifestyle factors, or other reasons. BUA may be used by the physician along with other clinical factors in the diagnosis of osteoporosis and other conditions leading to reduced bone density.

When evaluating individual patients, all relevant risk factors should be considered. (Previous fractures, frame size, smoking, age etc.)

## 1.9 Patient counseling information

A Patient Information Package is available from your CUBAClinical supplier. This booklet provides an introduction to the condition of osteoporosis, the cause, treatment, and prevention and also explains the CUBAClinical measurement and report.

## 1.10 Conformance to Standard

There are no known adverse effects of this device on health. The ultrasound power levels used by the CUBAClinical are lower than standard imaging ultrasound devices which are widely used and accepted.

## 1.11 What is Supplied

The CUBAClinical shipping package includes the following :

- One CUBAClinical Unit
- One Padded carrying bag for the CUBAClinical unit
- One Serial Cable
- One Power Cable (the type supplied will be appropriate to the country of destination)
- One User's Manual
- One QA Phantom
- One Padded carrying bag for the Phantom
- CUBA plus+ V4 software installation disk/s
- One bottle of ultrasound gel
- Two inserts (for correctly positioning the patient's foot)

## 1.12 Quantitative Ultrasound (QUS) as a Tool for the Assessment of Bone Status

In the medical field, ultrasound is commonly used to obtain 2-dimensional soft tissue images. However, it may also be used to characterize the physical properties of cancellous (trabecular) bone.

Quantitative Ultrasound (QUS) possess advantages over the traditional techniques (radiographs, x-ray absorptiometry, computed tomography) for assessment of bone mass. QUS is quick, non-ionizing and low cost and it provides information relating to characteristics of bone (structure, elasticity) in addition to density, that are important in the determination of fracture risk.

Cancellous bone is eight times more metabolically active than cortical bone and age and disease related bone loss are more readily apparent at sites where there is a high percentage of this type of bone. The calcaneus (heel) is a bone that is 75 – 90% cancellous. There is little soft tissue surrounding the bone making it an excellent site for QUS measurement and hence the determination of a patients risk of fracture.

QUS measurements obtained using the CUBAClinical are compared to a normative database and expressed in terms of "T" score, "Z" score, and % expected (age matched). The T-Score and Z-Score values are also displayed graphically for quick and easy interpretation.

## 1.13 What the CUBAClinical Measures

The CUBAClinical measures two parameters, BUA (Broadband Ultrasound Attenuation) for clinical measurements and additionally VOS (Velocity of Sound) which is used in the QA test.

The more complex the structure of the bone, the more the sound wave will be blocked. Therefore, normal bone has a higher attenuation (BUA) than osteoporotic bone. Likewise the greater the connectivity of tissue, the faster the sound wave will pass through it. As bone becomes osteoporotic the architecture diminishes and the speed of the sound wave slows down.

BUA is compared to results obtained from a normative population and expressed graphically and in the following terms by % expected for the subjects age group, Z-Score, and T-Score.

## 1.14 CUBAClinical System Overview

The CUBAClinical is a portable ultrasound device that measures BUA of the calcaneus. These data are compared to a reference value in order to assess the bone status of the patient relative to race, age and gender. Reference values for Caucasian women are supplied with the System.

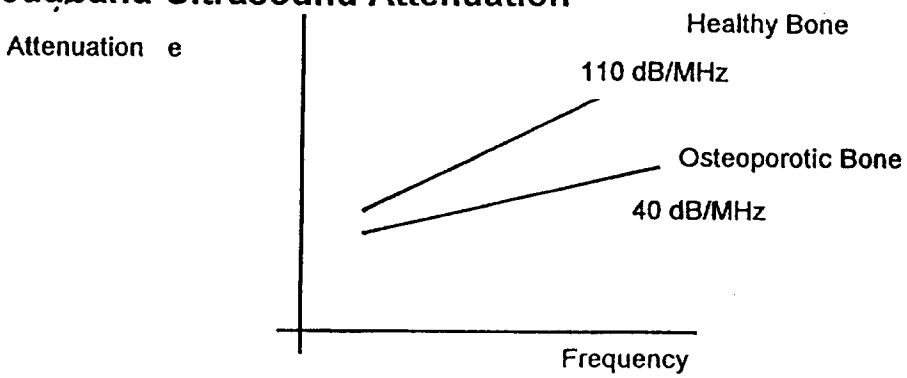
The measurement is taken with the patient seated. Their foot is positioned by use of an anatomical insert (based on foot length) and the foot and leg are secured by the use of two straps. The transducers are brought into contact with each side of the calcaneus, and acoustic coupling is achieved by the use of silicone pads and ultrasound gel. The silicone pads are permanently attached to the transducers and the ultrasound gel is applied prior to each patient measurement. A sound wave is passed through the heel taking only a few minutes to provide the patient with an indication of their fracture risk status.

The patient will be unaware of the measurement process as the sound waves produced by the CUBAClinical are outside the range of human tissue sensation.

## 1.15 Ultrasound Measurement Using the CUBAClinical

A high frequency (non audible) sound wave is passed from one transducer (the transmitter) through the heel to another transducer (the receiver). Acoustic coupling is achieved by the use of silicone pads and ultrasound gel. The parameter measured by the receive transducer is the attenuation of the received signal (BUA).

### Broadband Ultrasound Attenuation



The attenuation of ultrasound (dB) at a particular frequency (MHz) is defined as the ratio of signal amplitude (volts) for a reference material and the measured bone. There is a linear relationship between attenuation and frequency for cancellous bone between 0.2 MHz and 0.6 MHz to which a regression is applied, yielding the BUA index of units dB/MHz-1. The reference trace (a measurement through de-gassed water) is performed in the factory and stored within the CUBAClinical. The range of BUA observed with the CUBAClinical in a typical population is approximately 23 to 124 dB/MHz with young healthy subjects having a higher BUA than older osteoporotic subjects.

## 1.16 Relationship between CUBAClinical Results and Risk of Fracture

Prospective clinical studies have demonstrated that subjects with low BMD are at higher risk of fracture. The risk of fracture increases exponentially with decreasing BMD. For example, for Hip fracture, it has been demonstrated that with a 1 SD decrease in hip BMD there is a two to three fold increase in the risk of hip fracture. (A two fold increase is often reported as a relative risk of 2).

It has also been demonstrated that a similar relationship exists between heel ultrasound and hip fracture with approximately a two fold increase in the risk of fracture per 1 standard deviation (SD) decrease in BUA.

A recent prospective study using the CUBAClinical confirmed previous findings. A decrease of one SD in BUA was associated with more than a two-fold increase (2.3 RR) in hip fracture and a 60% (RR 1.6) increase in the risk of any fracture.

In summary, prospective studies have demonstrated the strong exponential relationship between heel ultrasound and x-ray results, and the ability of the CUBAClinical to predict the risk of future fracture.