P990039

SUMMARY OF SAFETY AND EFFECTIVENESS DATA

I. GENERAL INFORMATION:

Device Generic Name:	Ultrasound Bone Sonometer
Device Trade Name:	QUS-2 Calcaneal Ultrasonometer
Applicant's Name and Address:	Metra Biosystems 265 No. Whisman Rd Mountain View, CA 94043
Premarket Approval Application (PMA) Number:	P990039
Date of Good Manufacturing Practice Inspection:	5/5/00 (Metra) and 4/26/00 (Seamed)
Date of Notice of Approval of Application:	8/1/00

II. INDICATIONS FOR USE

The QUS-2 ultrasonometer is a medical device that utilizes quantitative ultrasound for evaluation of the calcaneus. Its BUA (broadband ultrasound attenuation) value is intended to be used as an aid in the diagnosis of osteoporosis and in the determination of risk of subsequent atraumatic fracture.

III. CONTRAINDICATIONS

None known.

IV. WARNINGS AND PRECAUTIONS:

The QUS-2 is a medical device and should be operated according to the instructions and specifications described in this manual.

The QUS-2 should not be used on subjects with breached skin (abraded skin) or open sores on the area of the foot that comes into contact with the system, including foot bed, heel post, front calipers and transducers. Doing so may increase the risk of transmission of infection between patients.

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General Precautions

Read the Operator's Manual before operating the QUS-2.

Never charge or discharge the battery near sparks or open flames. Always disconnect and remove the battery before transporting or shipping the QUS-2.

Avoid exposure of the QUS-2 to direct sunlight or temperature extremes during operation. Airflow from heating or cooling systems, where temperatures may exceed 95°F or drop below 60°F, may adversely affect system performance.

Never expose the QUS-2 to abrasive or corrosive materials, such as sodium hypochlorite (bleach), as contact may damage the instrument surfaces.

Never use the QUS-2 or its accessories in a manner other than indicated.

Only technically qualified personnel should perform troubleshooting and service procedures on internal components. Unauthorized access to internal components will void the warranty.

Keep hair and clothing away from moving parts to avoid injury.

Follow local governing ordinances and recycling plans regarding disposal or recycling of device components and packaging.

Patient Safety

Measurements using the QUS-2 should be performed only by a trained operator.

Do not leave patient unattended during the measurement procedure.

The QUS-2 is not intended for use on children.

Do not allow the patient to stand on the QUS-2.

Never connect the QUS-2 to a peripheral device, such as a computer, while a patient is in the vicinity of the QUS-2.

Operator Safety

Do not attempt to repair the QUS-2. The device contains no user serviceable parts other than the battery and printer paper.

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Never use liquids on or near the QUS-2 as contact with internal components may create a shock hazard. Do not operate the system if internal components have been exposed to fluid. Only exterior surfaces can be wiped with a damp towel or cloth.

Do not pick up the QUS-2 by the footbed or transducer arms. Lift the device by the base only.

Electrical Safety

Ensure that the system is connected to a grounded power receptacle that provides voltage and current within the specified rating for the system (120V, 240V). Use of an incompatible power receptacle may produce electrical shock and fire hazards.

Do not use a non-ground plug adapter to connect primary power to the system. Use of a non-ground adapter disconnects the utility ground, creating a severe shock hazard. Never alter or cut the instrument plug-in as this causes instrument damage and a shock hazard.

Only UL 2601-1 / CSA C22.2 No. 601.1 Classified Medical devices should be connected to the QUS-2.

V. DEVICE DESCRIPTION:

The QUS-2 Calcaneal Ultrasonometer assesses the quality of the calcaneus by sending a form of acoustic energy, known as ultrasound, from one transducer to another across the heel. By analyzing the ultrasound that traverses the heel, the QUS-2 determines the patient's calcaneal BUA that can be compared to the results from a young normal Caucasian female reference population. The result of this comparison, expressed in standard deviations, is called the T-Score. The T-score offers a convenient method for assessment of the calcaneus.

The QUS-2 features a variety of characteristics including the following:

Portability: The QUS-2 weighs approximately 7 pounds (3.2 kg) and is easily carried from one location to another. Scans can be conducted in the office, at the bedside, or any convenient location.
Scanning: The scanning technology of the QUS-2 allows reproducible and accurate measurement of the calcaneus without a positioning device.
The footbed accommodates both small and large feet.
Rapid Turnaround Time: A scan can be completed in less than two minutes.
Battery Operation: The QUS-2 can operate on rechargeable battery power or AC power, providing ultimate flexibility for the operator.
Dry Measurement: The QUS-2 is a dry ultrasound system.
Ultrasound Gel: The QUS-2 determination is performed with readily available water-soluble ultrasound gel.

A. Device Components.

The QUS-2 Calcaneal Ultrasonometer is a self-contained unit that can function without external computer support or an AC power outlet. The controls for operating the QUS-2 are located on the front panel. When the QUS-2 is operational, powered by either AC or battery, the "Power On" LED located in the lower left corner of the front panel is illuminated.
Messages are displayed on the LCD screen on the left side of the front panel. The keypad, located adjacent to the LCD screen, allows the entry of simple numerical responses, when prompted, to select the type of scan to be performed and to enter patient data. Once a scan is completed, the results are displayed on the LCD screen and are printed by the on-board printer located above the keypad.

The patient's foot is aligned in the footbed with reference to three points: heel post, foot calipers, and colored bar centering indicators. The footbed has an open design and fits either foot. During the scan, mobile transducers move along the patient's heel, sending a broadband ultrasound signal into the heel. The transducers locate and scan an area of approximately 1 cm^2 called the Region of Interest (ROI). The emerging signal is analyzed and the Broadband Ultrasound Attenuation (BUA) in decibels per megahertz (dB/MHz) is calculated. An individual's BUA result is then compared to a reference population for determination of a T-Score.

The footbed accommodates a foot of women's shoe size 5 to men's shoe size 12 (USA), or sizes 35-45 (European).

B. Device operation

The QUS-2 actively scans the heel to locate the trabecular-rich region of the calcaneus. When a patient's foot is placed in the QUS-2, the device transmits ultrasonic energy to locate the plantar and posterior edges of the calcaneus. Once these edges are identified, the transducers move to a pre-determined location where they begin to scan an approximately 1 cm^2 area rich in trabecular bone called the region of interest (ROI). Once identified, the QUS-2 makes 88 independent measurements within the region of interest to determine BUA. With its unique edge detection capability, the QUS-2 can reproducibly scan and assess the same trabecular-rich ROI within and across individuals. This means that QUS-2 can evaluate individuals with extreme foot size without aid of a positioning device.

The QUS-2 reports BUA that is estimated from a ultrasound measure known as UBI. QUS-2 captures only a few microseconds of signal and characterizes the bone's low-pass filtration without resorting to methods requiring lengthy continuous waveforms and the resultant imprecision. In simple terms UBI, which is expressed in microseconds, represents the "dominant early period" or

mean frequency of the signal traversing the heel during the first few microseconds of ultrasound transmission.

The actual ultrasound measurement takes approximately one minute to perform and the results are displayed on a liquid crystal display (LCD) panel and printed on the inboard thermal printer. Moreover, the design of the QUS-2 allows the user to periodically purge results from the memory or to download them to a computer. The power emission of the QUS-2 transducers is much less than the limit required for standard imaging devices set forth in the "Information for Manufacturers Seeking Marketing Clearance of Diagnostic Ultrasound Systems and Transducers (issued on September 30, 1997)." The QUS-2 Calcaneal Ultrasonometer System includes the device and all necessary accessories, including Operator's Manual, test object, ultrasound gel, battery, and power supply and cords.

VI. ALTERNATIVE PRACTICES AND PROCEDURES

The diagnosis of osteoporosis and assessment of fracture risk have conventionally relied on various radiation-based techniques. Methodologies based on ionizing radiation include single energy x-ray absorptiometry (SXA), dual energy x-ray absorptiometry (DXA), quantitative computed tomography (QCT), single photon absorptiometry (SPA), and dual photon absorptiometry (DPA). These techniques can be used to estimate the bone mineral density of virtually any skeletal site. Of these techniques, SXA and DXA are the most widely used. Other available methods are various types of bone sonometers employing ultrasound radiation.

VII. MARKETING HISTORY:

The Metra QUS-2 Calcaneal Ultrasonometer has been marketed in Australia, Brazil, Germany, Korea, Malaysia, Nepal, Taiwan, the United Kingdom, and Venezuela. The QUS-2 has not been withdrawn from any international market for any reason related to safety and effectiveness of the device.

VIII. POTENTIAL ADVERSE EFFECTS OF DEVICE ON HEALTH:

There are no known potential adverse effects of this device on health. Power levels used in this device are much lower than power levels of ultrasound devices widely used for imaging. No adverse events have been reported for the QUS-2 during clinical use, either from the clinical study reported in this submission or from systems installed internationally.

IX. SUMMARY OF PRECLINICAL STUDIES

A. In Vitro Precision

As a part of the clinical study described in the succeeding section, a protocol was developed and executed to determine the precision of the QUS-2 system response using a test object. All sites performed a verification of device calibration on each day of subject testing, using the Test Object provided with their QUS-2 device. In addition, all devices were quality control tested with a common phantom (QUS-2 Test Object) to quantitate inter-device system response differences. Four (4) measurements were taken for each device on the same day using this common test object. The average within-device standard deviation was calculated by averaging the variance for each of the 10 devices and taking the square root of the mean variance. The between-device standard deviation was calculated by taking the variance of the 10 device averages and taking the square root of that variance. The %CV were calculated by dividing the respective standard deviations by the overall average BUA values at two specific nominal BUA levels. Overall precision results, shown in Table 1, show marked agreement in system response between devices using a standard Test Object. Individual data points are given below.

Table 1: Precision of the Test Object at 2 BUA levels – 40 and 130 dB/MHz.

	Within Device		Between Devices	
	40 dB/MHz	130 dB/MHz	40 dB/MHz	130 dB/MHz
Variance	0.27	0.62	0.70	1.54
Std Dev	0.52	0.79	0.84	1.24
Avg BUA	39.91	129.60	39.91	129.60
%CV	1.29	0.61	2.10	0.96

B. Additional Studies

1. Biocompatibility

All the materials used in the production or operation of the QUS-2 have been selected such that they do not pose a biocompatibility hazard. The only materials which come into patient or operator contact are the footrest, heelpost, front calipers and transducer tips (patient) and ultrasound gel (patient and operator). The footrest is coated with Bayer FR-110 ABS polycarbonate Bayblend while the transducer tips are coated with Lustran ABS 633-2003. Both of these materials were demonstrated to meet the biocompatibility requirements of ISO10993/EN30993. The ultrasound transmission gel (Aquasonics-100, Parker Labs) is a water-based gel which is used in variety of ultrasound applications, including fetal and organ imaging. There are no known hazards associated with this gel.

2. Physics

Metra Biosystems provided test data for multiple QUS-2 transducers demonstrating maximum values of 0.13 for MI (mechanical index), 0.027 mW/cm^2 for $I_{spta.3}$ (derated spatial peak, temporal average intensity), 0.22 W/cm^2 for $I_{sppa.3}$ (derated spatial peak, pulse average intensity), and 0.015 mW for power. These results are within limits specified in the CDRH Guidance "Information for Manufacturers Seeking Marketing Clearance of Diagnostic Ultrasound Systems and Transducers," issued in September 1997.

3. Electromagnetic Compatibility

Metra Biosystems provided evidence demonstrating compliance with the emissions of EMC Directive (89/336/EEC) to the limits of EN 55011 for Group 1 Class B equipment. In addition, Metra also provided evidence of compliance with the immunity requirements of the EMC Directive (89/336/EEC) under the test conditions specified in IEC 801-2, IEC 801-3, IEC 801-4, and IEC 801-5 using the criteria defined in EN 60601-1-2.

4. Electrical Safety

The device consists of a plastic housing containing mechanical, electrical, and electronic components. Specific internal components include transducers, transducer motors, printed circuitry, a computer processor with software, battery, printer, and keypad with LCD panel. The QUS-2 conforms to UL 2601-1 Medical Electrical: General Requirements for Safety, CSA C22.2 No. 601.1, and EN 60601 requirements for patient connected devices.

5. Software

Software used in the QUS-2 was verified and validated under rigorous conditions using established testing procedures. These tests determined that operation of the QUS-2 is consistent with its specifications. Moreover, a hazards analysis indicated that all software and hardware user and patient concerns were adequately addressed.

6. Biological/Sterility

Labeling is provided for cleaning and disinfection, warnings, precautions, contraindications, indications for use, and adverse events in the Operator's Manual. The device is only to be used on intact skin.

X. SUMMARY OF CLINICAL STUDIES

Clinical studies were conducted to assess the safety and effectiveness of the QUS-2 Calcaneal Ultrasonometer as an aid in establishing the diagnosis of osteoporosis and assessing risk of osteoporotic fracture. The primary objectives of this trial were

- to directly compare broadband ultrasound attenuation (BUA) measured using the QUS-2 to BMD obtained using established dual x-ray absorptiometry for identification of osteoporosis and association to atraumatic fracture;
- to determine the distribution of BUA values across a wide age range in an apparently healthy female Caucasian population; and
- to evaluate the *in vivo* short-term precision of the QUS-2.

To establish this goal, three separate clinical trials were conducted at 10 clinical sites in the United States and Europe. The first objective was addressed in the safety and effectiveness trial, the second objective in the normal range study, and the third objective in the precision study.

A. Reference Population:
Female Caucasians 25 to 34 years of age with no history of osteoporosis or metabolic bone disease (Group 1).

B. Safety and Effectiveness Trial

The safety and effectiveness of the QUS-2 Calcaneal Ultrasonometer were evaluated in a 7- center cross-sectional clinical trial in which ultrasound and DXA results were compared in a population of Caucasian women. The study population consisted of 5 groups of subjects of varying age and skeletal status to facilitate evaluation of the QUS-2 and to insure a clinically relevant comparison of the two methodologies over a wide range of BMD. All subjects recruited to this study were female Caucasians, as this is the population most susceptible to osteoporotic fractures associated with compromised bone quality. Women meeting the inclusion and exclusion criteria who gave informed consent were invited to participate in the study as members of one of the following 5 groups defined according to age, WHO BMD classification[1], and fracture status:

Group 1: 25 to 34 years of age with no history of osteoporosis or metabolic bone disease (Reference Population).

Group 2: 50 to 84 years of age with normal bone mineral density and no history or evidence of atraumatic fracture.

Group 3: 50 to 84 years of age with osteopenia and no history or evidence of atraumatic fracture

Group 4: 50 to 84 years of age with osteoporosis and with or without history or evidence of atraumatic fracture

Group 5: 50 to 84 years of age with osteopenia or normal bone mineral and radiographically confirmed atraumatic fracture

Study procedures performed on subjects enrolled in this study included medical history, collection of anthropometric measures, dual x-ray absorptiometry of the lumbar spine and hip, and plane radiography of the lumbar spine for confirmation of fracture status (not required for subjects in Group 1). All measurements were performed on the right side unless fractures or other contraindications necessitated measurement of the left side. The primary variables of interest reported by the QUS-2 and DXA methods were BUA (in dB/MHz) and BMD (in g/cm^2) of the lumbar spine, femoral hip neck, and total hip. Classification into the clinical groups was based on BMD of the total hip. Variables analyzed and presented herein are abbreviated as follows.

AGE:	Subjects age (yrs)
BMI:	Body Mass Index (kg/m^2)
LSBMD:	Lumbar spine bone mineral density (g/cm^2)
LS T-score:	Lumbar spine T-score
FNBMD:	Femoral hip neck bone mineral density (g/cm^2)
FN T-score:	Femoral hip neck T-score
THBMD:	Total hip bone mineral density (g/cm^2)
TH T-score:	Total hip T-score
BUA:	Calcaneal broadband ultrasound attenuation (dB/MHz)
BUA-T-score:	Broadband ultrasound attenuation T-score

Conventional statistical analysis was performed to determine population averages, standard deviations, and ranges of the variables collected for Groups 1-5. T-tests (independent or paired as appropriate) or Analysis of Variance were used to determine statistical significance between various populations. Pairwise comparisons of significant ANOVA results were conducted using an appropriate a posteriori method. Regression was used to compare the QUS-2 BUA to the DXA BMD values. Clinical comparison of observed BMD and BUA results was facilitated by conversion of individual values to standardized deviates known as T-scores. T-scores were determined by normalizing an individual's BUA or BMD score to the average (device-specific) BMD or BUA (and its standard deviation) observed for the young reference range (T-score = $(BUA_{ind} - AVG_{ref\ range}) / STDDEV_{ref\ range})^2$. Receiver Operator Characteristics (ROC) analyses and odds ratios were computed to evaluate the association QUS-2 and DXA T-scores (e.g. -1.0, -1.5, -2.0, and -2.5) to outcomes of interest, e.g., fracture v. non-fracture.

A total of 699 female Caucasian subjects gave informed consent and participated in this evaluation of the QUS-2. Descriptive characteristics for the groups are shown in Table 2.

The strength of the association between calcaneal BUA BMD is dependent on anatomic site evaluated. Correlation between QUS-2 and BMD (at various anatomic locations) is shown in Table 3 and Fig.1. The correlation between QUS-2 BUA T-scores and BMD T-scores range from 0.5872 for lumbar spine to 0.6784 for total hip. These are somewhat less but comparable to the correlation between lumbar spine and either femoral neck or total hip. As might be expected the strongest correlation observed is between total hip and femoral neck.

Of the 699 subjects participating in the safety and effectiveness evaluation of the QUS-2, 171 comprised the reference range population, i.e., apparently healthy females between the ages of 25 and 34 years. Of the remaining 528 subjects, all of whom were between the ages of 50 and 84 years, 147 had clinical evidence of an atraumatic fracture. Of these 147 subjects, 117 had one or more vertebral fractures, 20 experienced fracture of the wrist, and 10 had evidence of hip fracture. For the purposes of comparing subjects with or without atraumatic fracture, only the 528 subjects in the target population (Groups 2 – 5) were included in the analysis.

Table 4 shows results for Age, BMI, LSBMD, LS T-score, FNBMD, FN T-score, THBMD, TH T-score, BUA, and BUA T-score stratified by presence or absence of atraumatic fracture. Subjects with fracture were significantly older, had lower estimates of BMD and BUA as well as lower T-scores than subjects without evidence of atraumatic fracture (all $p<0.0003$).

Table 5 shows the odds ratios and their 95% confidence intervals, as well as positive and negative predictive values at various T-scores for calcaneal BUA, and BMD of the lumbar spine, femoral neck, and total hip. In all cases the outcome of interest is the presence or absence of atraumatic fracture. As can be seen from Table 5, the results for BMD and BUA are significant and similar to one another at all cutoffs. As such, this indicates that the association of BUA as derived by the QUS-2 to atraumatic fracture is similar to DXA.

Receiver Operator Characteristic (ROC) curves were generated for T-scores for BUA and the DXA result for each anatomical site. Subjects without atraumatic fracture (Groups 2, 3, and 4) were compared to those with atraumatic fracture (Groups 4 and 5). To quantify the association of each measure to the outcome of interest, values for area under the curve (AUC), its standard error, and 95% confidence intervals were computed as shown in Table 6. The AUC's were not adjusted for the effect of age, which makes a significant contribution to the discrimination between fractured and non-fractured subjects. However, after adjustment for age by logistic regression analysis, BUA, as reported by the

QUS-2 ultrasonometer, was shown to be a significant independent assessment of fracture status. The ability of BUA to discriminate between these two populations is similar to that observed for DXA (of any anatomic site). Of greater interest is the comparison of subjects with and without atraumatic fracture, irrespective of group classification. The AUCs for comparison of subjects without atraumatic fracture (from Groups 2, 3, and 4; n=381) to subjects with atraumatic fracture (Groups 4 and 5; n=147) are statistically indistinguishable between diagnostic methods. The relationship was also observed even after 162 subjects with normal total hip BMD (Group 2) were removed from the analysis. Thus these ROC results provide further corroboration and demonstration of the similar association of BUA and BMD to atraumatic fracture.

Table 2: Summary of characteristics for the safety and effectiveness groups

Variable	Group 1	Group 2	Group 3	Group 4	Group 5	p-value
N	171	162	165	86	115	--
Age						
Avg	29.2	62.5	67.2	72.0	70.9	<0.0001
SD	2.9	9.5	9.2	7.5	8.9	
Range	25to34	50to84	50to84	52to84	50to84	
BMI						
Avg	23.4	29.2	25.2	22.8	27.7	<0.0001
SD	4.3	5.2	3.9	3.4	5.3	
Range	17.1to43.2	18.4to45.2	17.4to37.9	17.0to34.4	19.1to46.4	
LS BMD						
Avg	1.129	1.077	0.908	0.744	0.935	<0.0001
SD	0.138	0.177	0.141	0.132	0.168	
Range	0.808to1.633	0.721to1.681	0.591to1.268	0.353to1.127	0.592to1.378	
LS BMD T-score						
Avg	0.22	-0.27	-1.69	-2.99	-1.42	<0.0001
SD	0.95	1.34	1.15	1.12	1.37	
Range	-1.783.80	-2.96to4.17	-4.50to1.81	-6.31 to-0.40	-4.39to3.01	
FN BMD						
Avg	0.952	0.840	0.693	0.557	0.717	<0.0001
SD	0.132	0.109	0.081	0.078	0.10	
Range	0.684to1.332	0.646to1.209	0.522to0.915	0.403to0.784	0.534to1.069	
FN BMD T-score						
Avg	0.39	-0.56	-1.83	-2.88	-1.59	<0.0001
SD	0.93	0.76	0.54	0.63	0.90	
Range	-1.49to4.02	-2.10to1.90	-3.40 to-0.50	-4.20 to-0.89	-3.10 to 0.76	
TH BMD						
Avg	1.008	0.956	0.764	0.600	0.813	<0.0001
SD	0.113	0.084	0.055	0.048	0.118	
Range	0.822to1.335	0.821to1.357	0.638to0.869	0.389to0.688	0.637to1.145	
TH BMD T-score						
Avg	0.34	-0.10	-1.65	-2.91	-1.22	<0.0001
SD	0.87	0.67	0.40	0.37	0.90	
Range	-1.00to2.93	-1.00to3.00	-2.50 to-1.02	-4.54 to-2.52	-2.50-1.42	
BUA						
Avg	89.9	81.8	69.8	56.9	68.8	<0.0001
SD	11.9	13.4	13.3	11.6	14.7	
Range	59.0to130.7	49.7to123.3	40.3to109.3	34.6to86.0	40.3to120.2	
BUA T-score						
Avg	0.00	-0.69	-1.69	-2.77	-1.78	<0.0001
SD	1.00	1.13	1.12	0.9	1.24	
Range	-2.59to3.43	-3.38to2.81	-4.17-1.63	-4.64 to-0.33	-4.17-2.55	

Table 3: Correlations between T-scores from QUS-2 and DXA of the Lumbar Spine (LS), Femoral Neck (FN), and Total Hip (TH)[1]

Variable	LS T-score	FN T-score	TH T-score
LS T-score	--	--	--
FN T-score	0.7110	--	--
TH T-score	0.7469	0.9123	--
BUA T-score	0.5872	0.6643	0.6784

[1]All correlations statistically significant ($p<0.01$)

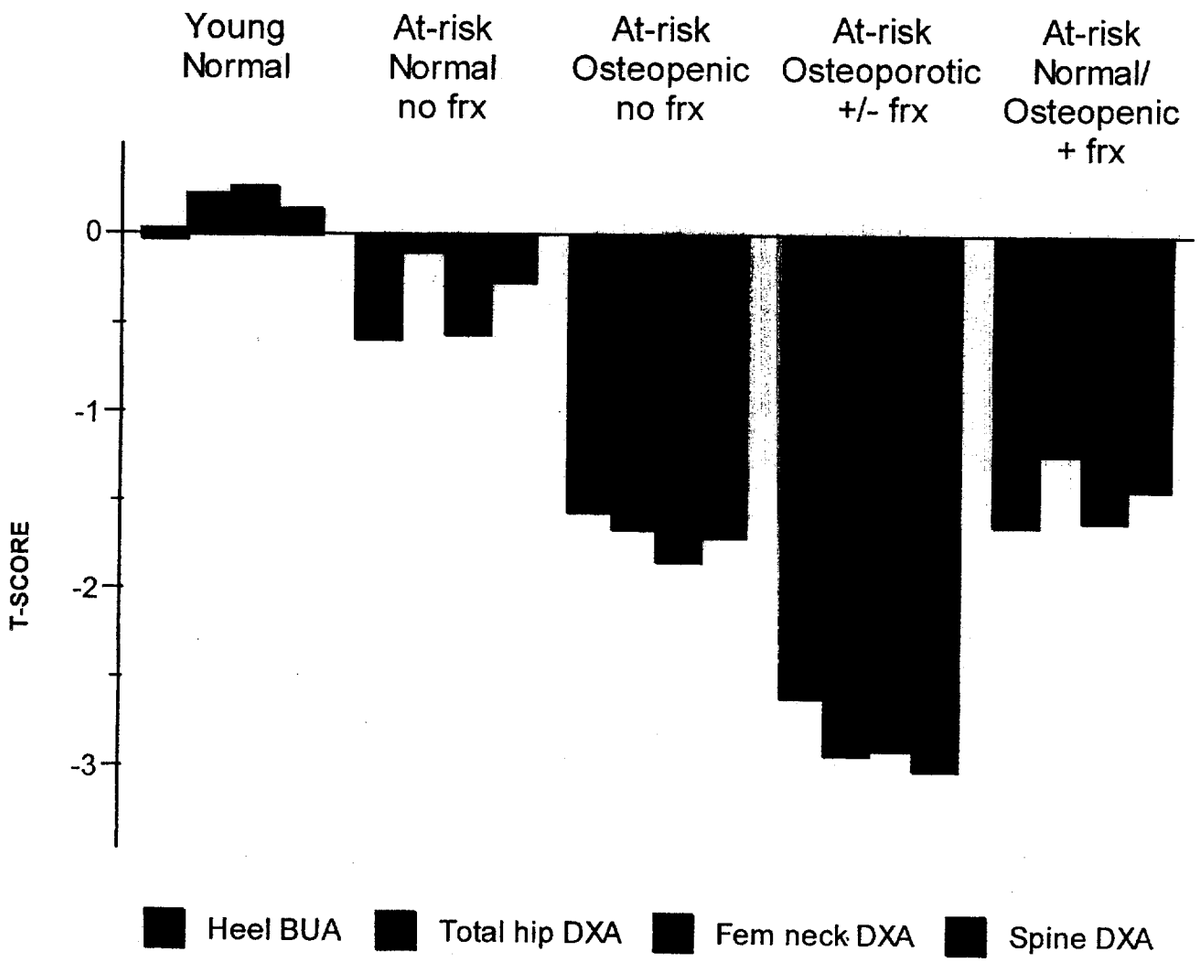

Figure 1: T-scores by method and group.

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Table 4: Comparison of Age, BMI, and measures of skeletal status stratified by presence or absence of atraumatic fracture

Variable	No Fracture	Fracture	p-value
N	381	147	--
Age (yrs)			
Avg	65.7	71.5	<0.0001
SD	9.6	8.7	
Range	50-84	50-84	
BMI (kg/m^2)			
Avg	26.7	26.4	0.538
SD	5.0	5.4	
Range	17.0-45.0	17.0-46.4	
LSBMD (g/cm^2)			
Avg	0.959	0.889	<0.0003
SD	0.192	0.183	
Range	0.515-1.681	0.353-1.378	
LS T-score			
Avg	-1.25	-1.79	<0.0003
SD	1.54	1.51	
Range	-4.84-4.17	-6.31-3.01	
FNBMD (g/cm^2)			
Avg	0.738	0.678	<0.0001
SD	0.136	0.134	
Range	0.403-1.209	0.450-1.069	
FN T-score			
Avg	-1.44	-1.90	<0.0001
SD	1.04	1.02	
Range	-4.01-1.90	-4.20-0.76	
THBMD(g/cm^2)			
Avg	0.824	0.764	<0.0001
SD	0.141	0.143	
Range	0.470-1.357	0.3989-1.145	
TH T-score			
Avg	-1.16	-1.62	<0.0001
SD	1.12	1.12	
Range	-3.87-3.00	-4.54-1.42	
BUA (dB/MHz)			
Avg	78.5	65.8	<0.0001
SD	17.5	14.2	
Range	29.3-127.2	34.3-111.2	
BUA T-score			
Avg	-1.26	-1.90	<0.0001
SD	1.24	1.24	
Range	-4.32-2.77	-4.38-2.52	

Table 5: Clinical Measures of association to fracture for T-score limits by method

Site	T-score	Odds Ratio	95% Conf Interval	Pred Value +	Pred Value -
Lumbar Spine BMD	-2.5	1.87	(1.23, 2.85)	38.1%	75.3%
	-2.0	2.00	(1.36, 2.95)	37.4%	77.0%
	-1.5	1.62	(1.10, 2.37)	32.8%	76.8%
	-1.0	1.60	(1.07, 2.40)	31.4%	77.7%
Femoral Neck BMD	-2.5	2.30	(1.48, 3.57)	42.5%	75.7%
	-2.0	2.34	(1.59, 3.46)	32.5%	73.7%
	-1.5	2.19	(1.47, 3.25)	29.4%	75.2%
	-1.0	2.55	(1.59, 4.11)	28.0%	78.1%
Total Hip BMD	-2.5	1.69	(1.04, 2.73)	37.2%	74.0%
	-2.0	2.02	(1.34, 3.04)	30.7%	71.9%
	-1.5	1.92	(1.31, 2.82)	29.2%	73.1%
	-1.0	2.12	(1.40, 3.22)	28.1%	81.0%
Calcaneal BUA	-2.5	2.81	(1.83, 4.33)	45.9%	76.8%
	-2.0	2.68	(1.82, 3.94)	41.0%	79.4%
	-1.5	2.97	(1.99, 4.41)	38.2%	82.8%
	-1.0	2.39	(1.54, 3.69)	33.4%	82.6%

Table 6. ROC Area* under the curve, its standard deviation and 95% Confidence Interval by method

Groups Compared		Method	AUC	SE	95% CI
Groups 2, 3, 4 (n=387)	Groups 4, 5 (n=147)	LS T-score	0.5967	0.0269	0.5432, 0.6484
		FN T-score	0.6307	0.0269	0.5769, 0.6821
Median age = 67	Median age = 74	TH T-score	0.6154	0.0269	0.5618, 0.6669
(Non Fracture)	(Fracture)	BUA T-score	0.6422	0.2666	0.5888, 0.6929

*not adjusted for the effect of age or any other relevant covariates
LS T-score = lumbar spine bone mineral density T-score, FN T-score = femoral neck bone mineral density T-score, TH T-score = total hip bone mineral density T-score, BUA = calcaneal broadband ultrasound attenuation T-score, AUC = area under curve from receiver operating characteristic curve, SE = standard area of AUC estimate; 95% CI = 95% confidence interval of the AUC estimate

C. Age Range Study

Protocol MU-83 (provided in Appendix 1b) describes a cross-sectional observational evaluation of the QUS-2 in approximately 623 apparently healthy, ambulatory Caucasian women between the ages of 35 and 84 years. The average and standard deviations of observed values will be used to 'normalize' results (determine Z-scores) from individuals participating in additional clinical studies. This data is intended to complement the safety and effectiveness evaluation of the QUS-2 (described in the MU-81 protocol and presented in Section III of this application) by providing information regarding age-associated changes in BUA.

Protocol MU-83 was conducted at 5 clinical sites, including 4 in the United States and a single site in Finland. Results obtained from 623 female Caucasian subjects between 35 and 84 years of age who gave informed consent and met the inclusion-exclusion criteria outlined in Protocol MU-83 are presented in this

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Appendix. Eligibility for inclusion in this study was similar to that employed in MU-81, however, subjects were not required to undergo dual x-ray absorptiometry for estimation of bone mineral density nor were subjects required to provide urine and serum specimens for determination of markers of bone metabolism. Pertinent data collected for the purpose of this application included body mass index (BMI), calcaneal BUA as derived by the QUS-2, and the resulting BUA T-scores. T-scores were generated using the average BUA and its standard deviation (89.0±12.4 dB/MHz) observed for subjects in Group 1 of Protocol MU-81 (apparently healthy Caucasian women between 25 and 34 years of age with normal skeletal health).

Results shown in this section are stratified by age in 10-year intervals as follows: 35-44, 45-54, 55-64, 65-74, and 75-84 years. The average, standard deviation, and range for BMI, BUA, BUA T-scores for each 10-year age interval are shown in Table 7. The distribution of BUA T-scores (including Group1 from safety and effectiveness study) is also shown in Figure 2.

Table 7: Descriptive statistics for BUA, BUA T-score, and BMI for all healthy subjects enrolled in the studies.

		Age Interval (yrs)					
		25-34	35-44	45-54	55-64	65-74	75-84
		171	124	128	121	123	123
BUA (db/MHz)							
	Avg	89.0	93.0	88.5	81.5	73.3	67.2
	SD	12.4	15.0	16.0	13.6	14.7	15.2
	Min	57.3	63.4	57.6	49.7	35.9	31.8
	Max	130.7	147.6	132.2	113.4	116.7	108.7
BUA T-Score							
	Avg	0.0	0.32	-0.04	-0.61	-1.26	-1.76
	SD	1.00	1.20	1.29	1.10	1.18	1.22
	Min	-2.56	-2.06	-2.52	-3.16	-4.27	-4.60
	Max	3.37	4.71	3.48	1.97	2.23	1.58
BMI (kg/m^2)							
	Avg	23.4	25.7	27.0	28.7	27.3	26.2
	SD	4.2	6.0	5.8	6.4	5.1	4.6
	Min	15.6	17.0	18.0	18.8	18.8	15.7
	Max	43.2	51.0	43.6	49.5	46.9	40.0

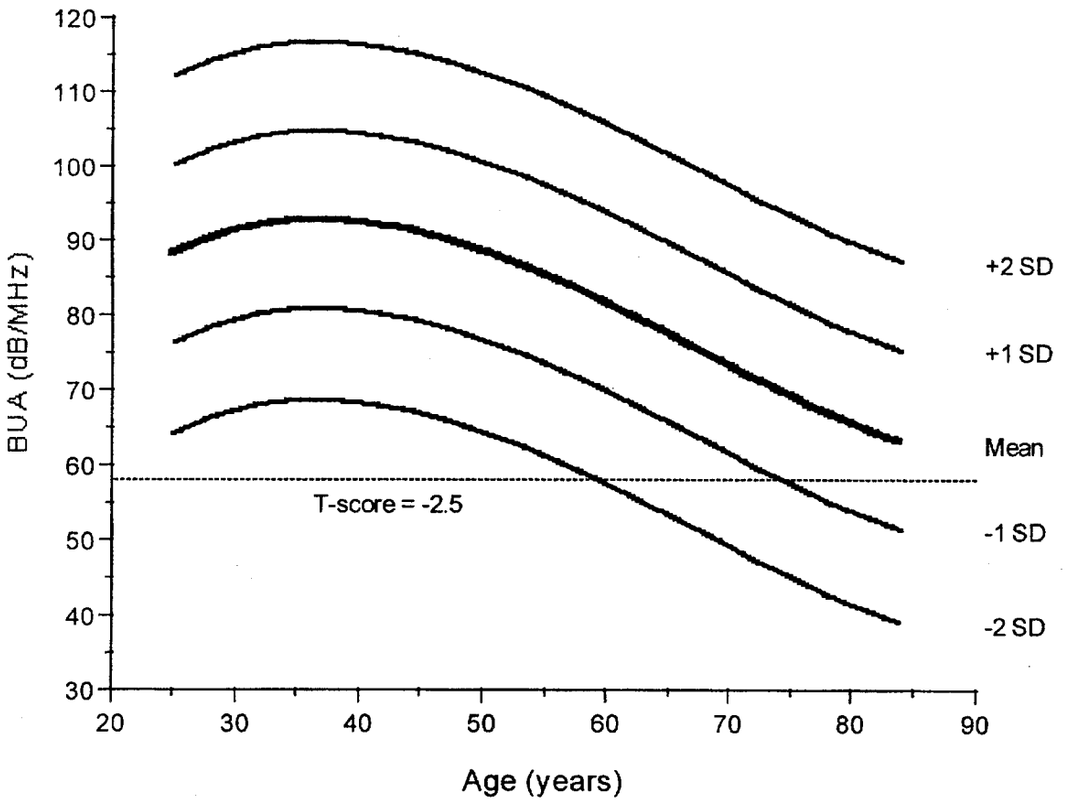

Figure 2: Distribution (Mean ± SD) of BUA by age.

D. Precision Studies

The short term (within-run) standard deviation was calculated by determining the variance for each timepoint, averaging these variances (all subjects and all sites), and taking the square root of the mean variance. %CV was calculated by dividing this short-term standard deviation by the overall average BUA. Data with repositioning of the foot between measurements was collected at all timepoints (see Table 8), whereas data without repositioning was from the baseline visit only.

Table 8: In vivo short-term precision of the QUS-2

Variable	Mean BUA (dB/MHz)	Standard Deviation	%CV	T-score Standard Deviation
Short Term (no repositioning)	83.0	2.11	2.52%	0.17
Short Term (with repositioning)	84.3	2.21	2.62%	0.18

XI. CONCLUSIONS DRAWN FROM THE STUDIES:

A. Risk/Benefit Analysis

The QUS-2 Calcaneal Ultrasonometer is a clinically useful tool for rapid and accurate assessment of skeletal status. Studies presented herein demonstrate that the ability of the QUS-2 to identify patients with osteoporosis and associated fracture is equivalent to DXA, but without exposure to ionizing radiation. Moreover, the power levels used by the QUS-2 are well within standards currently established for ultrasound-based medical imaging systems. Based on the clinical and non-clinical evidence presented herein, it is reasonable to conclude that the benefits of the QUS-2 outweigh the risk if illness or injury when used in accordance with the instructions provided in the Operator's Manual.

B. Safety

The safety of the QUS-2 Calcaneal Ultrasonometer has been amply demonstrated in this evaluation. In this triad of protocols, a total of 3392 scans were performed on 1391 subjects without any adverse events. This clinical experience, combined with the experience of other clinical evaluations of the QUS-2, is consistent with the absence or risks determined by a hazard analysis performed on the QUS-2 Ultrasonometer.

C. Effectiveness

Studies described herein amply demonstrate the ability of the QUS-2 to identify post-menopausal women with osteoporosis who are at increased risk for atraumatic fracture. These studies further demonstrate that use of the QUS-2 provides information regarding skeletal status that is clinically equivalent to estimation of bone mineral density. As such the BUA T-score can be used by a physician in conjunction with other risk factors to identify women at risk for osteoporosis and subsequent atraumatic fracture.

XII. FDA DECISION

CDRH issued the letter to METRA BIOSYSTEMS on August 1, 2000 advising that its PMA was approved on August 1, 2000. The manufacturing facility was inspected on May 5, 2000 (Metra) and April 26, 2000 (Seamed) and was found to be in compliance with the Good Manufacturing Practice Regulations (GMPs).

XIII. APPROVAL SPECIFICATIONS

Directions for use: See the labeling.
Hazards to health from use of the device: See Indications, Contraindications, Warnings, Precautions, and Adverse Events in the labeling.
Postapproval requirements and restrictions: See Approval Order.

XIV. REFERENCES

1. Kanis JA, Melton LJVIII, Christiansen C, Johnston CC, Khaltaev N. The diagnosis of osteoporosis. *J Bone Miner Res* 1994;9:1137, 41.

2. Looker AC, Orwoll E, Johnston CC Jr., et. al. Prevalence of Low Femoral Bone Density in Older U.S. Adults from NHANESIII, *J Bone Miner Res* 1997;12(11):1761, 1768.