1 SUMMARY OF SAFETY AND EFFECTIVENESS

1.1 General Information

Device Generic Name:	Obstetric Data Analyzer
Device Trade Name:	STAN® S31 Fetal Heart Monitor
Applicant Name:	Neoventa Medical AB
Applicant Address:	Agatan 32 SE-431 35 Moelndal Sweden
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Contact:	Mr. Simon Grant CEO Neoventa Medical AB
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Telephone:	202-546-1262 (202) 546-3848 (fax)
Contact Name:	Russ Pagano, Ph.D. or Marie Marlow
PMA Number:	P020001
Date of Notice of Approval to Applicant:	To be determined by FDA

1.2 Intended Use

The STAN system is intended to be used in pregnancies at term (>36 completed gestational weeks) to improve the assessment of the fetal condition during labor as an adjunct to standard fetal heart rate monitoring.

Use of the STAN system is indicated when there is planned vaginal delivery and:

- there is a need for close fetal surveillance during labor, or
- there are maternal disorders and/or utero-placental dysfunction with potential adverse influence on fetal oxygen and nutritional supply, or
- there is deviation from the normal course of labor including induction/augmentation of labor.

1.3 Device Description

1.3.1 Device Components

The STAN® S31 Fetal Heart Monitor is a fetal heart monitoring system used during labor and delivery to measure, display and analyze the ST waveform of the fetal ECG (FECG). The STAN System provides this ST waveform analysis as an adjunct to standard Electronic Fetal Monitoring (EFM/CTG) to provide doctors and midwives with more detailed information about the fetal hypoxic situation during labor.

The STAN System consists of a Main Unit, which physically consists of two modules, a Display Unit (DU) and Patient Interface Box (PIB) interconnected mechanically and by cabling. Included in the system are also patient sensors and embedded application software.

Fetal ECG and heart rate are measured continuously via a scalp or spiral electrode placed on the presenting part of the fetus and connected via a 'Legplate' connecting cable to the PIB.

The Legplate includes a connection for a skin electrode which is attached to the maternal thigh. This electrode provides a reference which is essential in obtaining the FECG waveform.

Uterine activity is measured either by an external transducer (TOCO) placed on the abdomen of the mother or by an intrauterine catheter connected via an adapter cable.

External ultrasound monitoring is a standard functionality in Electronic FHR monitoring. The STAN S31 is also capable of measuring fetal heart rate (but not ST) using an ultrasound transducer. Dual ultrasound transducers facilitate twin monitoring and it is possible to simultaneously monitor one twin with FECG (via the spiral electrode) and the other twin with standard EFM (via the external ultrasound transducer).

A spiral electrode is needed whenever FECG is to be measured.

1.3.2 General Technical and Physical Properties

The system is operator controlled by means of a touch-screen which is also used to display EFM and ST information in real-time. Patient information and notes can be entered from a keyboard. FHR and uterine activity signals are presented onscreen as is standard with traditional EFM.

When fetal ECG is recorded with a spiral electrode, changes in the T wave and the ST segment of the FECG are automatically identified and analyzed by the application software. The analysis is displayed in the lower section of the screen as a series of data points (ST 'crosses') and event markers. In addition, the system includes an Event log (to the left of the screen) where ST and other important events are described.

The ST analysis identifies patterns and changes in the T wave and ST segment and displays events based on the analysis of those changes. All events are stored in the Event Log. The user considers their interpretation of the standard EFM parameters together

with the ST analysis results. STAN Clinical guidelines help the physician or midwife decide what action to take clinically in different situations.

1.4 Contraindications, Warnings and Precautions

Contraindications:

Need for immediate delivery to avoid undue delay in situations such as:

- cord prolapse
- preterminal fetal heart rate changes
- marked fetal bleeding

Known maternal/fetal disorder when application of a fetal scalp electrode is contraindicated, such as:

- HIV
- Infectious hepatitis
- Active herpes zoster
- Known or suspected fetal coagulation disorder

1.5 Potential Adverse Effects of the Device on Health

No new or additional potential adverse effects are associated with use of the STAN system for electronic fetal monitoring beyond those which are already known for standard electronic fetal monitoring (e.g., risks associated with the placement of a scalp electrode).

1.6 Alternate Practices or Procedures

Electronic fetal heart rate monitoring with the data presented on a strip chart recorder is currently the most commonly used method for assessing fetal intrapartum well-being during labor. Auscultation of the fetal heart beats and palpation may also be used to assess the fetus during labor.

Intermittent fetal scalp pH, fetal oxygen saturation, and fetal scalp stimulation are also used as measures of fetal oxygen levels during labor.

1.7 Marketing History

Over 500 STAN devices have been sold. This includes approximately 350 S21 devices and 150+ S31 devices. The devices have been sold throughout Western Europe with Scandinavia, France and the UK accounting for a large percentage of sales. The device

has never been subject to a recall and has never been removed from the market in any country.

1.8 Summary of Preclinical Testing

1.8.1 Algorithms and Software

The STAN System Application Software controls the data handling during a recording. The two major components of the Application Software are:

- The Main Software running on the CPU on the Main Board in the Display Unit which handles high-level signal processing, user interaction, data presentation, and system control.
- The DSP Software running on the Digital Signal Processor on the DSP Board in the PIB which handles digital filtering.

A third software component, called the Kernel Software, is run on the Main Board.

The function of the STAN S31 is highly related to the graphical user interface of the Main Software running on the Display Unit. Data is displayed continuously on screen and also on paper if a local printer is connected. External ultrasound recording displays only the fetal heart rate, while internal recording using a spiral electrode can show the fetal ECG (FECG) wave-form.

Using FECG information, the STAN® S31 fetal heart monitor calculates and displays a T/QRS ratio obtained from the fetal ECG complex, and also indicates the incidence of deviant, “biphasic” ST waveforms. T/QRS ratio changes are constantly monitored and a message is printed in the event of any deviation.

There are 3 modes of operation:

- Recording Mode – the mode used to record data
- Signal Mode – used to check FECG signal quality
- Review Mode – used to review previously recorded data whilst recording

1.8.2 System Verification and Validation Testing

The STAN S31 System has undergone extensive verification, validation and safety testing. It is organized in the following different areas:

- System validation (clinical evaluations).
- System verification, complete system internally verified against requirements for system.
- System verification, complete system externally tested against requirements for system.

- Sub-system verification of hardware modules, verified against requirements for hardware modules.
- Software verification, software verified against requirements for software.
- Software validation, the software and related development validated against its intended use (to operate as part of the system).
- In addition risk management has been applied.

1.8.3 Device Safety Testing – Conformance to Standards

The STAN S31 Fetal Heart Monitor is designed to comply with the following standards:

Electrical safety:	EN 60601-1: 1990 + A1 and A12: 1993 + A2: 1995 + A13: 1996
EMC:	EN 60601-1-2: 2001
Electrical safety for system:	EN 60601-1-1: 2001
Biocompatibility:	ISO 10993-1: 1993

STAN has received the following certifications. These reports certify that STAN complies with the requirements of the specified standard.

- Certificate for European Product Safety
- IEC System for Conformity Testing and Certification of Electrical Equipment (IECEE) - CB Test Certificate
- Report of Electromagnetic Compatibility, EMC Test Report
- UL Medical Electric Equipment, Safety Test Results

1.8.4 Summary of Animal Testing

Over 30 years of animal research formed the basis for the clinical studies program outlined below. A summary of these studies is provided in the following table.

Reference: Rosen KG, Kjellmer I. Changes in the fetal heart rate and ECG during hypoxia. Acta Physiol Scand 1975;93:59-66

Date	Animals	Number of animals	Method of evaluation	Results	Conclusions
1971 - 1973	Guinea-pig fetuses Cat fetuses Lamb fetuses Anaesthetised term fetuses, acutely exteriorised and subjected to graded hypoxia.	20 3 3	Objectives To investigate the vagal influence on the fetal hypoxic bradycardia and to identify changes in the fetal ECG during graded hypoxia. Study outline The vagal influence of the fetal hypoxic bradycardia was tested by comparing the time for onset of bradycardia, with or without vagal activity. Precordial ECG was continuously recorded and used for FHR measurement and for identification of changes in the ECG waveform during graded hypoxia. Induction of hypoxia The mother was ventilated with a low oxygen gas mixture (3-10% O_2)	There was no indication of any vagal component in the fetal hypoxic bradycardia. Bradycardia is therefore to be regarded as a sign of myocardial hypoxia and failing fetal circulation. The ECG showed that the fetal bradycardia initially is an AV-block, type II. The data also showed that there are progressive changes in the ST interval as an early sign of hypoxia. Both an increase in the T wave amplitude, S-T elevations and negative T waves were recorded.	Continuous fetal ECG recordings during hypoxia showed that the fetal bradycardia is due to an AV-block, type II. There are progressive changes in the ST interval, which can serve as a most early sign of fetal hypoxia. Since the T wave represent myocardial repolarization, which is a metabolically active, energy consuming process, the rise in the T wave amplitude seen, could be a sign of rise in plasma potassium due to glycogen metabolism.

Reference: Rosen KG, Isaksson O. Alterations in the fetal heart rate and ECG correlated to glycogen, creatine phosphate and ATP levels during graded hypoxia. Biol Neonate 1976;30:17-24.

Date	Animals	Number of animals	Method of evaluation	Results	Conclusions
1974	Guinea-pig fetuses Anaesthetised term fetuses, acutely exteriorised and subjected to graded hypoxia.	40	Objectives To investigate how the depletion of glycogen, creatine phosphate and ATP in the fetal heart, liver and brain correlates with FECG changes during graded hypoxia. Study outline The depletion of glycogen, creatine phosphate and ATP in the fetal heart, liver and brain, were analysed in biopsy samples. ST interval changes were graded in a FECG scoring system, with an eight-graded scale, according to severity. The first fetus of each litter was immediately biopsied and served control for its littermates. Induction of hypoxia The mother was ventilated with a low oxygen gas mixture (8% O_2)	A strong linear correlation was found between the FECG scoring system and the depletion of heart glycogen and creatine phosphate. ATP was unaffected until glycogen was severely affected. Bradycardia was strongly associated with failing myocardial metabolism.	It is concluded that the changes in the fetal ECG pattern, could be regarded as a sign of myocardial glycogenolysis and early hypoxic stress.

Reference: Hökegård KH, Eriksson BO, Kjellmer I, Magno R, Rosén KG. Myocardial metabolism in relation to electrocardiographic changes and cardiac function during graded hypoxia in the fetal lamb. Acta Physiol Scand 1981,113:1-7.

Date	Animals	Number of animals	Method of evaluation	Results	Conclusions
1975-1976	Lamb fetuses Anaesthetised fetuses acutely exteriorised and subjected to graded hypoxia.	21	Objectives To analyse the metabolic background of hypoxic FECG changes. Study outline Serial myocardial biopsies in the fetal lambs were analysed for depletion of glycogen, creatine phosphate and ATP. FECG changes were also correlated to the myocardial performance measured by, FHR, mean arterial blood pressure, combined cardiac output and myocardial contractility (dP/dt). Induction of hypoxia The mother was ventilated with a low oxygen gas mixture (8-15% O_2)	During hypoxia there was a significant relationship between ST changes and depletion of myocardial glycogen. A highly significant correlation was seen between the amount of glycogen available and the increase rate in T wave amplitude. A parallelism was seen between the amount of available glycogen and fetal cardiovascular function. In the absence of acidosis and hypoglycaemia, the myocardium showed a remarkable good capacity to regenerate its glycogen stores during periods of adequate oxygenation.	The present results demonstrate a close correlation between the severity of changes in the fetal ECG and the depletion of myocardial glycogen stores. An accumulation of lactate occurs in parallel to glycogen depletion.

Reference: Hökegård KH, Karlsson K, Kjellmer I, Rosén KG. ECG-changes in the fetal lamb during asphyxia in relation to beta-adrenoceptor stimulation and blockade. Acta physiol scand 1979,105: 195-203.

Date	Animals	Number of animals	Method of evaluation	Results	Conclusions
1976	Lamb fetuses Anaesthetised fetuses acutely exteriorised and subjected to graded hypoxia.	14	Objective To investigate whether beta-adrenoreceptor stimulation and hypoxia exerted additive or potentiating effects of the FECG and several cardiovascular parameters. And to investigate if the hypoxic changes in the FECG could be blocked by beta-adrenoreceptor blocking agents. Study outline FECG changes were quantified according to a scoring system. The grades were then used for correlations with cardiovascular function; measured by FHR, mean arterial blood pressure, end diastolic pressure, blood gases, acid-base status, blood lactate and glucose. Beta-adrenoreceptor stimulation was induced by injection of isoprenaline (0.02 to 0.04 µg x kg^{-1} x min^{1}). Beta-adrenoreceptor blockade was induced by injection of propranolol. Induction of hypoxia The mother was ventilated with a low oxygen gas mixture (9-15% O_2)	Isoprenaline injection induced the same pattern of changes in FECG as previously recorded during hypoxia. By increasing the isoprenaline dose, an increase in the duration as well as the T wave amplitude were obtained. Propranolol completely abolished the FECG changes induced by isoprenaline as well as by mild hypoxia. During severe hypoxia, the FECG changes could not be abolished by propranolol.	The conclusion to be made is that mild hypoxia initiates the FECG changes via an activation of beta-adrenoreceptors while severe hypoxia induces FECG changes through a direct effect. Thus, progressive changes in the ST interval of the FECG during hypoxia seem to reflect the myocardial glycogenolysis induced by an imbalance between energy yield and energy consumption.

Reference: Dagbjartsson A, Herbertsson G, Stefansson TS, Kjeld M, Lagercrantz H, Rosén KG. Beta-adrenoceptor agonists and hypoxia in sheep fetuses. Acta Physiol Scand 1989,137: 291-299.

Date	Animals	Number of animals	Method of evaluation	Results	Conclusions
1981 - 1984	Lamb fetuses Anaesthetised fetuses acutely exteriorised and subjected to graded hypoxia.	17 controls 11 in the max group 7 in the 30 µg group 8 in the 10 µg group	Objective To test the influence of maternal beta-mimetic therapy on fetal reactions to hypoxia. Study outline Terbutaline was infused to the mother at three different dosages. In the 10 µg group the terbutaline concentration was in the therapeutical range (11-58 nmol/l). In the max and 30 µg group the terbutaline was (50-748 nmol/l) which is above the therapeutical range. Induction of hypoxia Intermittent complete occlusion of the maternal abdominal aorta.	Fetuses in the max group reacted to moderate hypoxia with excessive responses of heart rate, blood pressure, myocardial contractility and ST waveform changes. The mortality in this group was 50% compared to 12% for the controls. The 10 µg group did not have increased mortality, but the terbutaline caused an increase in myocardial workload and a negative energy balance during severe hypoxia. There was a close correlation between myocardial workload and the T/QRS ratio (r=0.73, $P<0.01$).	The data show that the fetal myocardial beta-receptors can be stimulated to their maximum capacity by high maternal doses of beta-agonist combined with hypoxia. Beta-agonist administration to the mother diminishes the fetal defence for hypoxia.

Reference: Greene KG, Dawes GS, Lilja H, Rosén KG. Changes in the ST waveform of the fetal lamb electrocardiogram with hypoxemia. Am J Obstet Gynecol 1982,144: 950-957.

Date	Animals	Number of animals	Method of evaluation	Results	Conclusions
1977 - 1979	Lamb fetuses During general anaesthesia the mother and the fetus were catheterised and electrodes for FECG analysis were implanted subcutaneous in the fetus. The ewe was then housed in the company with another ewe and was feed hay and concentrate, with free access to water and a mineral stone.	10	Objectives To study the effect of hypoxia on the ECG waveform in the healthy but chronically instrumented fetal lamb and to explore the possibilities of automatic sampling and quantification of ST waveform changes. Study outline The ST waveform of the fetal ECG in ten chronically instrumented fetal lambs was measured from day 115 to term. Averaged ST waveforms were plotted at 5 min intervals in six fetuses for 2 to 22 days. No diurnal or other rhythms were seen. T wave amplitude was measured in relation to the QRS amplitude as a T/QRS ratio. 20 hypoxia experiments were performed on seven of the fetuses between 120-139 days of gestation. Induction of hypoxia Hypoxia was induced for 1 to 2.5 hours at a time, by administration of a gas mixture of 7% or 9% O_2 and 3% CO_2 in N_2 to the ewe.	The T/QRS ratio was normally <0.30. Persistent T/QRS ratios between 0.32 and 0.65 preceded fetal death by some days in three fetuses and were associated with anaemia and/or hypotension in three other fetuses. In those animals hypoxia caused a further rise in the T/QRS ratio, mean from 0.48 to 0.81 and all died during labour. In the fetuses with normal ST waveforms there were differences in their respectively response to hypoxia, despite a similar drop in PO_2. In eight experiments the T/QRS ratio increased from 0.17 to 0.59 and promptly reverted to normal with normoxia. This was associated with a significant rise in mean arterial blood pressure, plasma lactate, glucose and fall in pH. In four experiments there was a moderate change in mean T/QRS, from 0.19 to 0.25, combined with a moderate increase in plasma lactate. Overall there was a strong correlation between T/QRS ratio and lactate levels.	These findings complement previous results in the acute fetal lamb preparation and suggests that ST waveform elevation, expressed as the T/QRS ratio, identifies a shift to anaerobic myocardial metabolism. No diurnal rhythms were seen.

Reference: Rosén KG, Dagbjartsson A, Henriksson BA, Lagercrantz H, Kjellmer I. The relationship between circulating catecholamines and ST waveform in the fetal lamb electrocardiogram during hypoxia. Am J Obstet Gynecol 1984,149:190-195.

Date	Animals	Number of animals	Method of evaluation	Results	Conclusions
1979 - 1982	Lamb fetuses Age during hypoxia experiments was 117-143 days of gestation. During general anaesthesia the mother and the fetus were catheterised and electrodes for FECG analysis were implanted subcutaneous in the fetus. The ewe was then housed in the company with another ewe and was feed hay and concentrate, with free access to water and a mineral stone.	7	Objectives To test the hypothesized relationship between the concentration of circulating catecholamines and T wave amplitude. Study outline The ST waveform of the fetal ECG, in seven chronically instrumented fetal lambs, was measured from day 117 to term. Averaged ST waveforms were plotted every 2 min. Blood sampling was done before induction of hypoxia and then every 20 min. 16 one-hour experiments with induced hypoxia were performed. T wave amplitude was measured in relation to the QRS amplitude as a T/QRS ratio. Induction of hypoxia Hypoxia was induced for 1 hour at a time, by administration of a gas mixture of 7% to 9% O_2 and 3% CO_2 in N_2 to the mother.	The response to hypoxia was age-dependent. Fetuses below 126 days of gestation did not react with FECG changes and epinephrine surge, unless acidosis occurred. In more mature fetuses, hypoxia per se induced a surge of epinephrine and ST waveform changes. Overall there was a strong correlation between the T/QRS ratio and the levels of circulating epinephrine (r=0.765, n=95, $P<0.001$) During normoxia, epinephrine was undetectable (<0.1 nmol/l) in most fetuses, whereas norepinephrine showed an increase at term. The data includes one fetus with chronic ST waveform changes (T/QRS >0.30). This was related to a marked increase in plasma epinephrine in spite of normal blood gas values. It was also shown that oxygen concentrations had to decrease by 64% before an adrenaline surge occurred and the T wave increased in amplitude.	These findings complement previous results in the acute and chronically instrumented fetal lamb preparations. It suggests that changes in the ST waveform expressed as T/QRS ratio identify a shift towards anaerobic myocardial metabolism, mediated by beta-adrenergic stimulation. Such a response seems to integrate well into the fetal reaction to hypoxia.

Reference: Rosén KG, Lilja H, Hökegård KH, Kjellmer I. The relationship between cerebral cardio-vascular and metabolic functions during labor in the lamb fetus and newborn. Academic Press, London. 1985.

Date	Animals	Number of animals	Method of evaluation	Results	Conclusions
1980 -1982	Lamb fetuses During general anaesthesia the mother and the fetus were catheterised and electrodes for FECG analysis were implanted subcutaneous in the fetus. The ewe was then housed in the company with another ewe and was feed hay and concentrate, with free access to water and a mineral stone.	2	Objectives To compare the different means of fetal surveillance with special emphasis on ST waveform analysis of the FECG during spontaneous labour in the chronically instrumented fetal lamb. Study outline The study presents two case reports of intrauterine death, due to fetal hypoxia. Somatosensory evoked EEG response (SEP), to assess the integrity of the fetal nervous system, was included in the chronically instrumented fetal lamb preparation. Case 1 Spontaneous labour at day 143 of gestation, 28 days postoperative. Case 2 Spontaneous labour at day 125 of gestation, 11 days postoperative. Induction of hypoxia Spontaneous stress during labour	Case 1 FHR was largely unaltered until the last 3 hours, and then a tachycardia occurred. Bradycardia and fall in blood pressure occurred during the last 5 min. Significant ST waveform changes occurred during the last 12 hours of labour. The T/QRS ratio increased progressively in parallel with increase in uterine activity and degree of hypoxia. The fetal brain maintained its functionality until the last 30 min. Brain death occurred 6 min before the last heartbeat. Case 2 In this less mature fetus, the T/QRS ratio increased from 0.30 to 0.80 between 14 and 9.5 hours prior to fetal death. Cortical activity as indicated by SEP was unaffected until the last 45 min.	These data indicates that the mature lamb fetus maintains its central nervous system integrity, until there are signs of cardiovascular collapse and that ST waveform changes were associated with intact fetal cortical activity and preceded fetal death by hours.

Reference: Greene KR, Rosén KG. Long term ST waveform changes in the ovine fetal electrocardiogram: the relationship to spontaneous labor and intrauterine death. Clin Phys Physiol Meas 1989, 10: 33-40.

Date	Animals	Number of animals	Method of evaluation	Results	Conclusions
1977 - 1982	Lamb fetuses During general anaesthesia the mother and the fetus were catheterised and electrodes for FECG analysis were implanted subcutaneous in the fetus. The ewe was then housed in the company with another ewe and was feed hay and concentrate, with free access to water and a mineral stone.	12	Objectives To study long-term changes in the FECG and the relationship between FECG changes and spontaneous labour and intrauterine death. Study outline An observational study where 12 catheterised animals were monitored. Three of them were monitored during spontaneous labour, six developed long-term ST waveform changes and three fetuses died during the postoperative period. Induction of hypoxia Spontaneous stress during labour	Uterine contraction was shown to, by themselves, induce increases in T/QRS ratio. If the ST elevation was normalised between contractions, the fetus seemed to compensate for the moderate hypoxia. When oxygenation was further reduced, the T wave remained elevated between contractions. During the final stage of labour, a progressive T/QRS increase was noticed. The lactate concentrations increased in parallel with the T/QRS increase. Long-term ST changes with T/QRS ratios >0.30 related to low haemoglobin levels and/or fetal hypotension. Subsequently, all these fetuses died during labour as compared to a 40% survival rate in fetuses showing a normal ST waveform. These fetuses displayed negative T waves as a sign of failing myocardial response to hypoxia. Death in uterus whatever the cause (bleeding, infection or spontaneous hypoxia) was always preceded by marked ST waveform changes.	It is concluded that ST elevations with high peaked T waves could appear on long-term basis in fetuses with intrauterine complications.

Reference: Widmark C, Hökegård KH, Lagercrantz H, Lilja H, Rosén KG. Electrocardiographic waveform changes and catecholamine responses during acute hypoxia in the immature and mature fetal lamb. Am J Obstet Gynecol 1989 May, 160(5): 1245-1250.

Date	Animals	Number of animals	Method of evaluation	Results	Conclusions
1985 -1987	Lamb fetuses During general anaesthesia the mother and the fetus were catheterised and electrodes for FECG analysis were implanted subcutaneous in the fetus. The ewe was then housed in the company with another ewe and was feed hay and concentrate, with free access to water and a mineral stone.	16	Objectives To investigate the changes in FECG and the release of catecholamines in fetal lambs of different maturity grades, during nonacidaemic fetal hypoxia. Study outline The study contained two groups of chronically instrumented lamb fetuses, an immature group (119 to 126 days, n=10) and a mature group (129 to 141 days, n=6). Hypoxia was induced and PO_2, pH, PCO_2, catecholamines and FECG were followed during hypoxic experiments. Induction of hypoxia Obstruction of maternal placental blood flow through complete obstruction of the maternal aorta for 60 seconds.	Both groups of fetuses had a marked fall in oxygen tension (immature 2.43 ± 0.12 to 1.46 ± 0.12 and mature 2.22 ± 0.15 to 1.11 ± 0.17 kPa). Oxygen saturation dropped from 48% ± 3% to 17% ± 2 in the immature group and from 49% ± 3 to 15 ± 3 in the mature group. Only modest changes occurred in pH and PCO_2. Basal catecholamine concentration did not differ between the groups, but it increased more significantly in the mature group during hypoxia. An increase in T wave amplitude occurred in both groups during the latter part of occlusion. In the mature group a linear correlation was found between plasma epinephrine concentration and T/QRS ratio. Fetuses of both groups showed a marked bradycardia of similar magnitude during occlusion, but differed during recovery. The mature group had a slower acceleration of the heart rate. During bradycardia, the mature fetuses responded with a significant rise in mean arterial blood pressure.	The study suggests that fetal maturity has a significant influence, not only on the release of catecholamines during nonacidaemic hypoxia, but also on the cardiovascular reaction pattern and changes in the ST waveform.

Reference: Widmark C, Jansson T, Lindecrantz K, Rosén KG. ECG waveform, short-term heart rate variability and plasma cathecholamine concentrations in response to hypoxia in intrauterine growth retarded guinea pig fetuses. J Develop Physiol 1991,15:161-168.

Date	Animals	Number of animals	Method of evaluation	Results	Conclusions
1988 - 1989	Guinea-Pig fetuses At mid term the doe was anaesthetised and one uterine artery was ligated on one side. She was then allowed to recover and pregnancy would continue until 63 days of gestation. The doe was then anaesthetised a second time. The fetuses were acutely exteriorised and subjected to graded hypoxia by letting the doe breath a low oxygen gas mixture.	24	Objectives To study the ST waveform of the FECG, short-term heart rate variability and plasma catecholamines in normal and growth retarded fetuses, during hypoxia. Study outline The study was done on 12 growth retarded fetuses and 12 of their normal littermates. FECG and short-term heart rate variability were studied during normoxia and in response to acute hypoxia. Blood was sampled and blood gases, acid-base status and catecholamine concentrations were analysed. Induction of hypoxia Hypoxia was induced by letting the doe breath a low-oxygen gas mixture.	The T/QRS ratio was normal and similar in both groups prior to the hypoxic periods. In the normal sized group, T/QRS ratio increased as a response to hypoxia. The growth retarded fetuses presented a completely different pattern. Seven out of twelve fetuses showed a biphasic ST waveform, with depression and downward sloping ST segment and negative T wave, during hypoxia.	The study indicates that hypoxia induced FECG waveform changes, differ between intrauterine growth retarded guinea-pig fetuses and their normal sized littermates.

1.9 Summary of Clinical Studies

1.9.1 Prior Clinical Studies

Feasibility Studies

Several published clinical studies were conducted as feasibility studies prior to initiation of the Swedish Randomized Controlled Trial (SRCT). All were conducted under Ethical Committee approval and patient informed consent.

These feasibility studies addressed issues regarding the ability to evaluate ST waveform changes during labor, the positive predictive value between CTG plus elevated T/QRS ratio compared to fetal acidemia during labor and delivery, and evaluations of improvements in signal processing.

The studies demonstrated the feasibility of using ST waveform analysis as an adjunct to standard fetal heart rate monitoring to improve the assessment of the fetal condition during labor. As a result, the studies were used to help develop the design of the Swedish Randomized Controlled Trial (SRCT) which is one of the pivotal studies conducted in support of the STAN PMA application.

The Plymouth Study: An Early Randomized, Controlled Study

Successful feasibility studies led investigators to conduct a large, randomized controlled trial in a non-academic setting to collect scientific evidence of the clinical value of fetal ECG (CTG) + ST waveform analysis. This study was conducted at Freedom Fields Hospital in Plymouth, England. The Plymouth Study tested the hypothesis that the combination of ST waveform and CTG analysis, compared to CTG analysis only, would reduce operative interventions for fetal distress without placing the fetus at risk.

A STAN prototype was used to test this hypothesis. A total of 2400 patients enrolled in the study. Results demonstrated a significant reduction ($p<0.001$) in operative deliveries for fetal distress without increasing the risk of hypoxia. The study was therefore successful in achieving its objective.

Additionally the study demonstrated a trend toward reduction in babies born with metabolic acidosis and low 5 minute Apgar scores. But the study was not sufficiently powered to show a statistically significant difference in these two endpoints

The Gothenburg Study: A Post-SRCT Study

Subsequent to the successful completion of the Swedish Randomized Controlled Trial (discussed below), evaluation of the STAN Fetal Heart Monitor was continued in Gothenburg, Sweden. A prospective, observational study was conducted at two maternity wards located at Sahlgrenska University Hospital and the district general hospital at Moelndal.

Between October 2000 and September 2002, a total of 4830 high-risk deliveries were monitored using the STAN S21 Fetal Heart Monitor. The study assessed the value of the STAN monitor for intrapartum fetal monitoring using cardiotocography (CTG) and ST waveform analysis. The Characteristics of the monitored pregnancies, categorized by first and second year of the study are described in the following Table.

Table VI. A: Characteristics of patients monitored

Time period	First year	Second year	
Total number of term deliveries in active labor	7325	7362	
	STAN monitored		
Total	2057	2773	p<0.0001
>42 weeks	15.9%	15.2%	ns
Nullipara	63.8%	64.1%	ns
Pre-eclampsia	5.5%	4.1%	ns
Hypertonia	2.0%	1.7%	ns
Gestational diabetes	2.7%	3.8%	ns
Induction of labor	20.8%	23.0%	ns
Oligohydramnios	4.6%	6.8%	ns

A comparison between the first and second year showed use of the STAN Fetal Heart Monitor increased from 22% to 38%. The increase in usage was correlated to an overall reduction in metabolic acidosis rate from 0.77% to 0.44% in the total population, the same low incidence of hypoxic neonatal encephalopathy as noted in the SRCT and no increase in operative interventions for fetal distress. This later finding is important because it is in contrast to established findings that the use of conventional CTG is associated with an increase in operative interventions.

The study investigators conclude that, with continued use and experience, the STAN Fetal Heart Monitor provides consistent improvement in fetal outcome. Study findings corroborate the results of the Swedish RCT and investigators conclude that STAN is a safe and effective medical device.

The EU Project: A Post-SRCT Series of Studies

The European Centers of Excellence project (EU project) was supported by the EU commission as an Innovation Grant (IPS-1999-00029). Initially, 10 academic institutions across Europe were included in the project. The Gothenburg Study, discussed above in section VI.A.3, was the first in this series of studies. These centers of excellence became the regional hub of experience – Centers of Excellence. The project started in 2000, finished in 2002 and included approximately 8000 fetal monitoring recordings. Since the initial group was established, more Centers of Excellence have been established. This project was not a clinical investigation. The STAN Fetal Heart Monitor was used as part of normal clinical management practice at each center. Integral to the EU Project was a structured education and training program.

The EU Project established the success of the training program and that upon training and certification, STAN users are able to use the STAN Fetal Heart Monitor according to its intended use to improve assessment of the fetal condition during labor as an adjunct to standard fetal heart rate monitoring.

Canadian Post-Swedish RCT Study

This study was conducted by the University of Western Ontario, Ontario, Canada. The STAN Fetal Heart Monitor was used to collect ST wave-form information from a total of 143 patients for retrospective analysis of the data. Only fetal heart rate information was used for clinical management of the patients. Retrospective analysis of the ST-wave form was conducted by two study investigators.

The authors conclude that the number of neonates with metabolic acidemia at birth was almost equally distributed between those in whom STAN clinical guidelines dictated intervention and those in whom STAN clinical guidelines did not dictate intervention.

The outcomes from this study are not consistent with those of the Swedish RCT. Several reasons for these differences include the use of a standard spiral scalp electrode that had not previously been tested for ST analysis (resulting in ECG signal loss) and interpretation of STAN indications out of clinical context.

1.9.2 Pivotal Studies

Three prospective clinical studies were submitted in support of the STAN PMA application. These studies are:

1. The Swedish Randomize Controlled Trial. This clinical trial is a pivotal study that demonstrates safety and effectiveness of the STAN fetal heart monitor.
2. The US Education Study. This validation study demonstrates the ability of US obstetricians to understand and apply the STAN concept of ST analysis.

3. The US Clinical Use Study. This clinical study is a pivotal study that demonstrates statistically significant agreement between US obstetric staff and OUS expert STAN users in the clinical management of labor using the STAN fetal heart monitor.

These three studies are summarized below.

1.9.2.1 Swedish Randomized Control Trial (SRCT)

Introduction

The STAN® fetal heart monitor is a digital signal processing technology that, applied to the fetal electrocardiogram (ECG) recording taken during intrapartum internal monitoring, identifies and analyzes changes in the T wave and ST segment. The technology is based on the recognition that an increase in T wave amplitude, in relation to QRS amplitude, corresponds to the utilization of glycogen stores and therefore also to myocardial anaerobic metabolism. Since anaerobic metabolism is the prime fetal defense against hypoxia, the T/QRS ratio provides direct information about the fetal situation. The STAN system provides an analysis of these changes during labor and thereby assists the obstetrician in identifying a situation requiring immediate intervention.

Purpose

Prior prospective and observational clinical studies indicate that analysis of the ST waveform of the fetal electrocardiogram (ECG) provides information on the fetal response to hypoxia. Information from these studies led investigators to hypothesize that intrapartum monitoring with Electronic Fetal Monitoring (EFM) combined with ST waveform analysis results in an improved perinatal outcome as compared with EFM alone. This hypothesis was tested in a multicenter randomized controlled trial conducted in Sweden by the Sponsor, Neoventa Medical AB.

The objective of the study was to evaluate the ability of obstetric clinicians and midwives to use ST information and very specific clinical guidelines to monitor labor and make clinical management decisions that would result in a reduced number of fetuses being born with metabolic acidosis.

The trial was conducted according to internationally recognized clinical trial guidelines, including the Declaration of Helsinki. Institutional approval was obtained prior to study initiation and patient informed consent was given by all study participants. Because this study was conducted in Sweden, an Investigational Device Exemption Application was not filed with the U.S. FDA.

Endpoints

Primary outcome

The main outcome variable, metabolic acidosis at birth, was defined as a cord artery blood pH <7.05 and a base deficit in the extracellular fluid compartment (BD_{ecf}) >12.0 mmol/L, using the Siggaard-Andersen Acid Base Chart algorithm. (Siggaard-Anderson O. An acid base chart for arterial blood with normal and pathophysiological reference areas. Scand J Clin Lab Invest 1971;27:239-45.)

Secondary outcome

The secondary outcome variable was the rate of operative deliveries (cesarean sections, forceps or ventouse deliveries) for fetal distress (ODFD). In addition, the neonatal morbidity was evaluated in terms of a) Apgar scores at 1 and 5 minutes and b) admissions to the Special Care Baby Unit (SCBU) also known as Neonatal Intensive Care Unit (NICU) in the United States.

Procedures

Prior to patient enrollment, researchers were trained to use the STAN fetal heart monitor. The education consisted of lectures, written information, and multimedia-based teaching, including a simulator module displaying previously recorded cases with ST-analysis. At each center, a research midwife was appointed to conduct the training, to support the staff during the trial and to verify the data entries into a computerized database. The regular labor ward staff (in all more than 300 obstetricians and midwives) managed all women included in the trial. Research Ethics Committees at the respective University approved the trial. All participating women gave their informed consent before entering the study.

Patients were randomized in a 1:1 ratio to either the CTG-only (control) group or to the CTG+ST (treatment) group. Cardiotocography (CTG) is the term used in the Swedish RCT. This term refers to Electronic Fetal Monitoring (EFM). When describing the SRCT, the term CTG is used rather than EFM.

Patients in the CTG-only group were monitored throughout labor using standard CTG practice. STAN fetal heart monitors were used for patients in the CTG-only group, but the ST analysis was not displayed on the monitor. ST information was stored in the computer database so the ST events could be retrospectively analyzed in the CTG-only group. This information was used to determine how many cases with adverse or complicated neonatal outcome in the CTG-only group could have been delivered earlier and how much earlier delivery could have been performed.

Patients in the CTG+ST group were monitored throughout labor using CTG interpretation supplemented by ST waveform. Specific CTG+ST Clinical Guidelines were used to interpret fetal status and manage labor. The Guidelines identify ST changes that indicate the need for clinical intervention. Intervention was always indicated for cases displaying a pre-terminal CTG recording.

All patients that entered the study were to have the umbilical cord artery and vein acid-base status assessed at delivery. Cord acid-base was used to provide a marker of the hypoxic process. The cord was to be double-clamped before or at time of first breath.

An alternative was to puncture the artery and vein directly at delivery. Acid-base analysis was to be made within 30 minutes.

Inclusion and Exclusion Criteria

Inclusion criteria:

- Women in active labor
- Term (more than 36 completed gestational weeks)
- Singleton fetus
- Cephalic presentation
- Use of EFM during active labor with clinical need for a fetal scalp electrode to provide continuous internal ECG recording.

At all investigational sites, clinical reasons that prompted internal fetal monitoring as the preferred method of surveillance included women with suspicious or abnormal external fetal monitoring, induced or oxytocin augmented labor, meconium stained amniotic fluid, or epidural analgesia.

Exclusion criteria:

- Delivery so rapid that less than 30 minutes of first stage or only second stage recordings are obtained
- Women using TENS (Transcutaneous Electrical Nerve Stimulatory) because STAN signal quality may be seriously impaired while TENS is being used as an on-going method of analgesia
- Pregnancies where gross fetal abnormality is recognized prior to labor.

Planned Analyses

Two outcome analyses were performed: An analysis of outcome was conducted strictly according to intention-to-treat, i.e. without any exclusions and a second analysis was conducted with the exclusion of neonates with severe malformations and inadequately monitored cases - those monitored for less than 20 minutes and cases where the monitoring was interrupted more than 20 minutes before delivery (cases defined as exclusions prior to study initiation). This analysis of adequate recordings was justified on the following basis; the device needs at least 20 minutes to establish a baseline T/QRS-ratio. Also, cases with severe malformations and those without monitoring during the last period before deliveries were considered to obscure possible associations between monitoring and outcome. For these reasons, analyses were performed both according to intention-to-treat and according to adequate recordings.

Study Population, Period, Sites and Investigators

Study Population:

4966 women in active labor with a single term (>36 completed gestational weeks) fetus in cephalic presentation were entered into the SRCT after a clinical decision had been made to apply a fetal scalp electrode for internal cardiotocography (CTG) recording. They were randomized to monitoring with CTG plus ST-analysis (treatment) or CTG-only (control). Clinical action was guided by the study protocol.

A total of 4966 patients entered the trial between December 1998 and June 2000, of whom 2447 were randomized to the CTG-only group and 2519 to CTG+ST. The numbers of women recruited for the study at each center correspond to 36 %, 31 % and 33 % of all women delivered during the study period in Lund, Malmö and Gothenburg, respectively.

Study Period:

Ethical committee approval was received for all three sites in June 1998. Patient enrollment was conducted during 18 months (December 1, 1998 to June 4, 2000) at three major labor wards in Sweden.

Study Sites and Investigators:

- University Hospital, Lund (in 1999: 2829 deliveries, perinatal mortality 8.2 per 1000, cesarean section rate 12.5 %)
- University Hospital, Malmö (in 1999:3220 deliveries, perinatal mortality 4.0 per 1000, cesarean section rate 13 %)
- Sahlgrenska University Hospital, Gothenburg (in 1999: 4229 deliveries, perinatal mortality 6.5 per 1000, cesarean section rate 14.7 %)

More than 300 obstetricians and midwives, trained to use the STAN fetal heart monitor, managed the 4966 patients who enrolled in the clinical study. The physician overseeing the entire SRCT was Prof. Karel Marsal, Department of Obstetrics and Gynecology at Lund University Hospital in Sweden.

Principal investigators were:

Lund University Hospital, Sweden

- Isis Amer-Wåhlin, MD
  Department of Obstetrics

Malmö University Hospital, MAS, Malmo, Sweden

- Per Olosson, MD, PhD
  Department of Obstetrics

Gothenburg, Sahlgrenska University Hospital/Östra, Sweden

- Håkan Lilja, MD, PhD
  Department of Obstetrics

- Håkan Norèn, MD
  Department of Obstetrics

Subject Exclusions

Protocol Deviations

The interim analysis scheduled after 1600 cases revealed protocol violations. These included

a) disregarding the recommendation to intervene according to CTG+ST guidelines and
b) intervention delayed or done without regard to the guideline recommendation.

Information gathered from the interim analysis resulted in retraining. During retraining, the protocol deviation cases were discussed along with other cases from the trial. In response to the retraining, protocol deviations in the CTG+ST group decreased. Eight protocol deviations occurred in the CTG+ST group and 8 protocol deviations occurred in the CTG-only group.

Device Malfunctions

Technical problems occurred in 48 cases. The majority of these problems was due to 1) user failure; addressed by providing additional user information, and 2) dysfunction of the external uterine activity sensor; addressed by replacing a faulty sensor. None of the technical problems created a safety issue for the patient or the device user.

SRCT Analyses

A total of 4966 patients entered the trial. There were 2447 patients randomized to the CTG-only group and 2519 to CTG+ST. There were 283 patients excluded from the CTG-only group and 291 excluded from the CTG+ST group due to fetal malformations or inadequate recordings.

STAN Effectiveness Data

Outcomes, analyzed according to intention-to-treat (all patients enrolled) are as follows:

- A significant reduction in the rate of metabolic acidosis at birth: 15 cases (0.69%) occurred in the CTG+ST-group and 31 (1.49%) cases in the CTG-group (OR 0.46, 95%CI 0.25-0.86, p = 0.02).
- A significant reduction in operative deliveries for fetal distress (ODFD)(OR 0.81, 95%CI 0.66-0.99, p = 0.047).
- No significant difference in the rates of operative deliveries for other indications (in most cases failure to progress, ODFTP between the two groups.
- The significant differences in ODFD and metabolic acidosis between the two groups occurred after retraining had taken place and when local cases were

discussed on a regular basis, with feed-back and expert opinions obtained, OR 0.62, 95%CI 0.46-0.85, p=0.002 and OR 0.33, 95% CI 0.11-0.98, p=0.045, respectively.

Outcomes, analyzed according to adequate recordings (283 patients excluded from the CTG-only group and 291 excluded from the CTG+ST group) are as follows:

- Significantly fewer cases of metabolic acidosis in the CTG+ST-group than in the CTG group (0.57% vs. 1.44%, p=0.01)
- Significantly fewer cases of ODFD in the CTG+ST-group than in the CTG group (5.9% vs. 8.0 %, p=0.009)
- Significantly lower rate of cesarean sections for fetal distress in the CTG+ST-group than in the CTG group (1.93 vs. 2.91%, p=0.04)
- As with intention-to-treat analysis, the improved outcome was significant only after retraining with a 44% reduction in ODFD (p=0.0013) and 72% reduction in the number of cases with cord artery metabolic acidosis (p=0.032).

STAN Safety Data

There were no adverse events related to the safe use of the device during the study.

The clinical risks are minimal and related to situations where:

- No ECG signal is available. In the rare situation where no signal is available, the clinician should revert (as per the labeling) to standard electronic fetal monitoring.
- The clinical management guidelines are not followed. Information from the SRCT has been used to develop a major training program to teach all STAN users how to use the clinical guidelines and thereby reduce the potential for an adverse clinical outcome.

SRCT Conclusions

The results from this study demonstrate that monitoring term fetuses with CTG combined with ST waveform analysis leads to a statistically significant improvement in perinatal outcome. This is the first study to demonstrate the safety and effectiveness of a new fetal monitoring methodology capable of reducing the risk of babies being exposed to severe intrapartum hypoxia, reducing the number of unnecessary operative deliveries for fetal distress and reducing the number of neonates born with signs of moderate/severe neonatal encephalopathy.

This study found that the rate of metabolic acidosis at birth was significantly reduced with CTG+ST-monitoring, compared with CTG alone. When analyzed according to adequate readings, the CTG+ST (treatment) group compared to the CTG-only (control) group, showed a

- 61 % reduction in the number of cases with umbilical artery metabolic acidosis (pH< 7.05 and base deficit >12mmol/L) (p=0.01);

- 78 % reduction in cases with metabolic acidosis admitted to special care baby unit (SCBU) (p=0.04);
- 27% fewer operative deliveries for fetal distress (p=0.009; and
- 88% fewer neonates with signs of moderate/ severe neonatal encephalopathy (OR 0.12, 95% CI 0.01-0.94; p = 0.02).

The rates of operative interventions for failure to progress did not differ between the two groups. During the second half of the clinical trial, investigators became more proficient in their abilities to interpret the ST analysis and manage labor according to specific guidelines unique to ST analysis. With proficiency, results from the second half of the trial led to a greater reduction in cord metabolic acidosis (75 %) and operative deliveries for fetal distress (44 %).

Data from this study demonstrates that intrapartum monitoring with CTG combined with ST waveform analysis increases the ability of obstetricians to more appropriately intervene in cases of a non-reassuring fetal status during labor as compared to use of CTG-only.

1.9.2.2 U.S. Education Study

Introduction and Purpose

This study was performed as a validation study to evaluate the ability of US obstetric staff who are experienced in the application and interpretation of conventional intrapartum electronic fetal heart rate (FHR) monitoring to understand and apply the STAN concept of ST waveform analysis. This was achieved by training and certifying study participants, then assessing their ability to consistently and accurately interpret intrapartum tracings containing FHR-only and FHR + ST waveform data relative to the need to intervene upon labor.

The training and certification program used in the US Education Study reflects the same training and certification program used for the Swedish Randomized Controlled Trial (SRCT). This allowed for direct comparison of results between US study participants and Swedish STAN experts.

In summary, the purpose of the education study was to demonstrate that US obstetricians, nurses and midwives can be trained to interpret and use the STAN concept of ST waveform analysis correctly.

Endpoints

Primary Endpoint

The primary endpoint is the average consensus of US study participants. Consensus is defined as the proportion of US raters who agree to intervene on cases where intervention is warranted plus the proportion of US raters who agree not to intervene on cases where

intervention is not warranted. Adequate training is demonstrated if consensus improves with the addition of STAN information to conventional FHR information.

Secondary endpoints were also considered: 1) consensus of the US participants incorporating time of intervention, and 2) median time of intervention.

Procedures

Thirteen U.S. obstetric staff members experienced in the application and interpretation of standard intrapartum electronic fetal heart rate (FHR) monitoring were evaluated according to study protocol to determine their ability to understand and apply the STAN concept of ST analysis.

Each participant received the US version of STAN teaching materials (Textbook and CD-ROM) to review before the study. A tutorial (including case discussions) followed this review (self-study). The tutorial was conducted by a team from Neoventa (the same for all sites). After the tutorial, the reviewers took a certification test to certify that they are capable of using the STAN data for intrapartum assessment.

Participants were required to examine a library of 51 FHR tracings consisting of complete cases in which the STAN system has been used. The tracings contain both normal and abnormal outcome cases in the approximate proportions they occur in labor units where high-risk care is provided. The traces are of variable length with the minimum tracing length being 2 hours and the maximum being 4 hours. The distribution of normal and abnormal cases is as follows:

- 9 cases had cord artery pH<7.05 (17.64%)
- 10 cases had cord artery pH between 7.05 and <7.15 (19.61%)
- 32 cases had cord artery pH≥7.15 (62.75%)

The first 9 cases are those that should warrant intervention. The second 10 cases are those that might have been intervened upon and the last 32 cases are those that should not warrant intervention.

Each US participant examined 51 tracings three different times.

1. The first examination was done before the STAN tutorial and case discussions were conducted (STAN training) and each tracing was examined using only FHR information. This first examination of the 51 tracings served as a control before training. Satisfactory completion of a certification test was required before proceeding to the following steps 2 and 3.
2. The second examination was done after STAN training and each tracing was examined using only the FHR information. This second examination serves as a control after training.
3. The third examination was done after STAN training and each tracing was examined using both FHR and ST information.

For each tracing at each examination time, the study participant determined whether or not the tracing indicated a need for delivery intervention and if so, the time of delivery intervention. The second and third examinations were performed at the same sitting,

sequentially for each tracing. This was to ensure that any variability in intervention status for a particular tracing within reviewer between the second and third examinations was due to the addition of the ST information to the FHR information and not due to external biases or information.

Correct interpretations of the 51 tracings were established by a panel of 7 Swedish obstetric clinicians who are considered to be experts in the clinical use of the STAN fetal heart monitor.

Inclusion Criteria

Study participants were required to be obstetric personnel with different levels of training (MD, RN or midwife). All participants were required to be experienced in the interpretation of conventional intrapartum FHR monitoring tracings and intrapartum care.

Planned Analyses

Analyses related to the primary and secondary endpoints were as follows:

Primary Analysis

A paired t-test was used to determine if the average consensus of US study participants using FHR+ ST information (third examination) is significantly greater than the average consensus of US study participants using FHR-only information (second examination) after education. A statistically significant result will indicate that consensus improves with the addition of ST information, and that US obstetric staff can be trained in the use of STAN.

Secondary Analyses

A paired t-test was used to determine if the average consensus incorporating time of intervention using FHR + ST information (third exam) is significantly greater than the average consensus incorporating time of intervention using FHR-only information (second exam) after education. A statistically significant result will indicate that consensus incorporating time of intervention improves with the addition of ST information, and that US obstetric staff can be trained in the use of STAN.

Study Population, Period, Sites and Investigators

Study Population

The study population consisted of obstetric personnel with different levels of training (MD, RN or midwife). All participants were experienced in the interpretation of conventional intrapartum FHR monitoring tracings and intrapartum care.

Study Period

The study was conducted during May 2003.

Study Sites and Investigators

The study was conducted at three US sites:

- Medical College of Georgia: Lawrence Devoe, MD., PI
- Winthrop State University Medical Center: Dev Maulik, M.D. PhD, PI
- Hospital of Saint Raphael, 1450 Chapel Street, New Haven, CT 06511: Wilfred Reguero, MD.

Protocol Deviations

Three protocol deviations occurred during this study. Three doctors failed the certification test but continued to perform assessments two and three. Per protocol, a participant should not have proceeded to the second and third assessments without having passed the certification test. All of the main analyses are based on all 13 raters who performed the assessment regardless of whether they passed the certification test. However, supplemental analyses, including an analysis of the primary end-point, are presented on only the 10 raters who passed the certification test.

Analyses

The primary endpoint was to document improvement in consensus with decision to intervene (yes or no) comparing the second FHR assessment (assessment 2) with the FHR+ST assessment (assessment 3). The capacity of ST analysis to improve fetal assessment among US raters was demonstrated by a statistically significant improvement in total accuracy from 53% to 69% ($p<0.001$).

Among the secondary endpoints, median time to intervention for FHR + ST (assessment 3) was within 20 minutes of that for EU experts in 8 out of the 9 cases requiring interventions (pH<7.05). It should be noted that the US version of STAN clinical guidelines would recommend an intervention somewhat sooner in one case in the <pH 7.05 group. Furthermore, consensus among the US raters was about the same for two FHR only examinations in situations with pH<7.15. However, in the group with pH ≥7.15 training improved the detection of normality.

Consensus with regard to intervention decision and timing for FHR + ST (assessment 3) as compared with FHR only (assessment 2) increased significantly from 43% to 59% in the acidotic group. Although there was no difference in general agreement among the majority of raters of the need to intervene in the acidotic group (pH<7.15) regardless of FHR-only or FHR+ST information, the ability to respond in a uniform way increased significantly when ST information was added.

Overall, the Educational study demonstrated the US obstetric staff to be highly sensitive to the combination of FHR+ST events with the decision of the majority of the raters to intervene when required in all cases. In cases of prolonged and obvious FHR abnormality the US raters tended to respond with interventions in spite of no ST events.

Conclusions

As a result of successful validation, the US education study protocol was used to develop the training program for the first phase of the US Clinical Use Study (conducted under G020290), a pivotal study that demonstrates statistically significant agreement between US obstetric staff and OUS expert STAN users in the clinical management of labor using the STAN fetal heart monitor.

1.9.2.3 U.S. Clinical Use Study (CUS)

Protocol: Clinical Use Study

Introduction

The Clinical Use Study (CUS) was conducted in response to FDA's request for a clinical validation study to demonstrate that US clinicians, using the US education program, can use the STAN Fetal Heart Monitor as intended.

Purpose

The purpose of this study was to demonstrate that US clinicians can appropriately use the STAN system, ST information and clinical guidelines to monitor labor and make clinical management decisions. The study was designed to demonstrate that US clinicians experienced in conventional fetal monitoring can use the STAN system in a manner comparable to that of experienced STAN users. The study was also designed to demonstrate that the STAN system data can be properly used according to clinical guidelines yielding results similar to the results seen in the Swedish RCT.

Endpoints

The primary endpoints were:

- US clinicians' correct decision to not intervene as determined by a cord artery pH level greater than 7.12 , and
- Agreement of US clinicians with STAN experts on deciding whether or not to intervene.

To demonstrate safety of the STAN system, a detailed analysis of any infant born with pH <7.15 was included.

Study Design Overview

The study was a multicenter non-randomized clinical trial conducted in three phases:

Phase 1, the Education/Certification Phase
Phase 2, the Pilot Phase, and
Phase 3, the Pivotal Phase.

Phase 1 – Education and Certification

The objective of this phase was to educate participating clinicians in STAN methodology and basic physiology using the STAN education program. Before proceeding to the next phase of the study, a participant was required to pass a certification test at the completion of the education program. The education program consists of:

- Textbook and interactive CD that cover basic physiology related to fetal hypoxia and fetal surveillance during labor;
- Interactive on-site tutorial and training that consists of lectures and case discussions from the database of completed cases;
- Certification test that includes 18 multiple choice questions. Questions cover interpretation of recordings and basic principles of intrapartum hypoxia and monitoring; and
- Continuing education on an Internet site (www.fecg.st) where key cases are followed by detailed case discussions to stimulate further interest in understanding the process of fetal monitoring.

Phase 2 – Pilot Phase

The objective of Phase 2 was to allow clinicians who passed the certification test to gain experience with the STAN concept and technology by using the STAN system as a standard Electronic Fetal Monitoring (EFM) device. ST information was available, but not used to manage cases.

All participating clinicians at each site were required to use the STAN system to monitor a minimum of 5 cases. The participating clinician completed a Pilot Phase Case Report Form for each case. These CRFs were reviewed by the site Principal Investigator and Neoventa to ensure that STAN technology was understood. Site clinicians participated in regular case discussions to further the understanding of STAN methodology.

To proceed to Phase 3, participating clinicians completed a credentialing process to become clinical investigators. The credentialing process included:

- successful completion of the Certification Test in Phase 1
- review and discussion of case tracings and CRFs with Neoventa or the PI to ensure understanding of the STAN concept and methodology
- demonstration of an understanding of STAN technology by producing

tracings of acceptable quality, all of which were to be reviewed by Neoventa. For a STAN tracing to be of acceptable quality, it must be >30 minutes in length with a part of the recording occurring within 20 minutes of delivery.

Phase 3 – Pivotal Study

The purpose of this Phase was to demonstrate that US clinicians who have become certified clinical investigators can use STAN system information and clinical guidelines to monitor labor and make clinical management decisions in a manner comparable to that of experienced STAN users.

The participating clinician completed a Pivotal Phase Case Report Form for each case. Three STAN experts retrospectively reviewed all cases and made a decision for intervention or not. The STAN experts used the US version of the Clinical Guidelines for review and recorded their findings on the STAN Expert Case Report Form. This information was used to assess agreement between the STAN experts and US clinicians.

Inclusion and Exclusion Criteria

Once a woman in active labor at term was assigned to have a standard fetal scalp electrode, she was eligible for inclusion in the study. A decision to include a patient in the study was made during the first stage of labor when the patient had time to understand the issues regarding the study.

Inclusion criteria:

- Singleton gestation
- Vertex presentation
- In active labor
- Term (>36 completed gestational weeks)
- Use of electronic fetal monitoring during active labor with need for application of a fetal scalp electrode.

Exclusion criteria:

- Women using TENS (Transcutaneous Electrical Nerve Stimulator), as signal quality may be seriously impaired while TENS is being used as an on-going method of analgesia.

Primary Analyses

The analysis of primary endpoints was performed based on all data available for the STAN recordings.

The first primary endpoint, the probability that non-intervention results in a normal outcome in the cohort of infants with non-reassuring FHR tracing (NRFHR) (i.e., the negative predictive value (NPV)), was tested using the hypothesis that the NPV in the cohort is greater than 75%.

H_0: $P_{NPV} < 75\%$vs. H_A: $P_{NPV} > 75\%$

NPV is defined as:

Numerator: # cases with NRFHR, ST data allow continued labor, there is no intervention and pH > 7.12.

Denominator: total # cases with NRFHR, ST data allow continued labor.

This hypothesis was tested using a one-sided one-sample binomial test. 95% confidence intervals were also calculated.

For the primary endpoint relating to percent agreement of US Clinicians with the STAN experts for cases that require "true intervention" (positive percentage agreement (PPA)), a study of 500 cases with a prevalence rate for positive cases of 9% would have 80% power to show PPA >75%, assuming the true PPA is 90%. Accordingly, for negative percent agreement (NPA) (*i.e.,* level of agreement in cases where the STAN experts decide not to intervene), 500 total cases would be sufficient to show that with 80% power NPA >75%, assuming the true NPA is 80%. All statistical significance was assessed using an alpha level of 0.05.

Secondary and Additional Analyses

The following secondary analyses were included. No quantitative thresholds of success were preset for these endpoints:

- Case-based analysis of all cases with cord artery pH <7.15
- Comparisons of operative intervention rates of clinical investigators before and during the study (if data were available).
- Analysis of all cases with NRFHR. Traces scored as to the sequence of FHR patterns (normal, grade 1, grade 2) and the extent to which STAN indications had been present.
- Analysis of the relationship between cord artery pH ranging from 7.10 to 7.15 and corresponding NPV in NRFHR cases not intervened upon.
- Comparison of US clinician/STAN experts will be summarized with regard to "true" intervention/no intervention and cord artery pH (<7.05; 7.05 – 7.14; >7.14).
- Analysis of primary endpoints will be stratified by clinical investigator to assess what proportion would meet the primary endpoints.

An early analysis was performed and submitted to FDA on the first 200 pivotal phase cases in order to verify the initial assumptions for sample size calculations. The early analysis showed that the rate of NRFHR cases with adequate cord blood gas data and without intervention due to STAN indications was 41.6%. Based on these results, the sample size of 527 was calculated and believed to be adequate to ensure 219 of this type of case were obtained.

Report: Clinical Use Study

Phase 1, Education/Certification

A total of 42 potential investigators were certified. Additionally 180 other staff received training, including site coordinators who were certified and trained as 'local trainers'. Most of the other staff were nurses or midwives who received training so that they could be better informed and support the practical, not clinical, handling of STAN on the ward. They were educated in STAN methodology and equipment using a subset of the STAN education program. Certification was not mandatory for the other staff, however 22 of the other staff took the test and were certified out of interest.

All investigators and local trainers completed the on-site training and passed the user certification test. Investigators transitioned into the Pilot Phase of the study between May 2004 and October 2004.

Phase 2 – Pilot Study

The goal of the pilot phase was to allow clinical investigators to become accustomed to the device by recording a minimum of 5 cases each. No patient management issues other than monitoring for adverse events were considered. A total of 207 adequate pilot phase recordings were performed at the 6 participating centers. All investigators used the STAN system and completed a Pilot Case Report Form for a minimum of 5 recordings.

All sites completed the pilot phase. All sites transitioned into the pivotal phase between August 2004 and November 2004.

STAN Pilot Phase Safety Data

There were no cases of perinatal metabolic acidosis and thus no cases of adverse events were noted. There was one infant with an Apgar score <7 at 5 minutes but no signs of perinatal asphyxia.

Phase 3 – Pivotal Study

Study Period, Sites and Investigators

A total of 530 STAN recordings on 530 subjects were collected during the pivotal phase at the 6 investigational study sites between September 12, 2003 and February 3, 2005. The "Investigators and Enrollment" Table shows the number of STAN recordings performed at each site along with the number of investigators and the number of recordings performed per investigator.

The activity of clinical investigators with regard to number of cases enrolled is a reflection of the clinical situation. One of the investigators had 57 recordings related to the investigator being in over all charge of the labor and delivery suite and responsible for high-risk case management.

Table 5: Investigators and Enrollment per Site

	STAN Recordings		Investigators		Range of Recordings Per Investigator
Site	**N**	**%**	**n**	**%**	
MCD	25	5%	2	5%	12 - 13
KWC	64	12%	5	13%	8 – 21
MCG	117	22%	11	28%	1 – 20*
SLC	161	30%	10	26%	7 – 32
UCL	105	20%	5	13%	8 – 57
WUH	58	11%	6	15%	1 – 13*
Total	530	100%	39	100%	1 – 57

*Three investigators had fewer than 8 recordings at site MCG and one investigator had fewer than 8 recordings at site WUH.

Protocol Deviations

A number of patients were excluded due to issues related to recordings (failure to start a recording, short recording). Protocol deviations included failure to obtain fully or appropriately signed Informed Consents, or associated HIPPA documents.

In one case, the patient had a private physician (not an investigator) attending the labor along with a study investigator. The study investigator consented the patient and put her on the STAN. The study investigator then left the room and the labor and delivery proceeded under the management of the private physician. The patient was included in the analysis.

Blood gases were not always collected from patients in the study. These patients were dropped from the study analysis relating to any blood gases. None of these cases was dropped from the analysis and all study documentation was retained.

Four investigators, three at site MCG and one at site WUH, performed fewer than the 8 recording minimum required per the protocol. Additionally, two subjects did not meet the eligibility criteria due to having fewer than 36 gestation weeks. These six patients were included in all analysis where there were data available for the case.

Device malfunctions

Device malfunctions included CMS interfacing problems, a failure of a MO disk drive and incorrect setup of one device. All problems were resolved. Problems were also observed related to the FSE legplates and these were exchanged out as the problem occurred. There were no adverse events associated with device malfunctions.

CUS Analysis

Primary Endpoints: NPV and PPA/NPA

Negative predictive value (NPV) was identified as the first primary endpoint to demonstrate that the application of STAN guidelines did in fact identify cases of acidemia and acidosis.

The NPV was calculated on the basis of cases where there was a non-reassuring FHR trace and a cord artery pH and where STAN guidelines had not been used to decide for intervention.

NPV was calculated for cases with pH values from <7.05 to < 7.15 for cases with non-reassuring FHR and no intervention undertaken according to STAN guidelines.

Negative Predictive Value by Cord Artery pH Cutoff

Cord Artery pH Cutoff	N	Abnormal pH	NPV	95% CI NPV	P-Value**
< 7.10	189	4	97.9%	(94.7%, 99.4%)	<.0001
< 7.11	189	5	94.2%	(93.9%, 99.1%)	<.0001
< 7.12	189	7	96.3%	(92.5%, 98.5%)	<.0001
< 7.13	189	9	95.2%	(91.2%, 97.8%)	<.0001
< 7.14	189	11	94.2%	(89.8%, 97.1%)	<.0001
< 7.15	189	14	92.6%	(87.9%, 95.9%)	<.0001

*Total NRFHR and No Intervention with Cord Artery pH Available
**Based on the null hypothesis that NPV ≤ 75%.

The NPV primary outcome measure of pH<7.13 was 95.2% with a 95% confidence interval (CI) of (91.2%, 97.8%) which met and ***exceeded*** the expected study outcome of >75%.

NPV by Site

	MCD	**KWC**	**MCG**	**SLC**	**UCL**	**WUH**	**Total**
Recordings	25	64	117	161	105	58	530
- Reassuring FHR	18	21	62	94	63	33	291
- Cord Artery pH N/A	0	4	5	5	9	1	24
- Intervention Performed	1	3	4	4	5	9	26
Total NRFHR and No Intervention with pH Available	**6**	**36**	**46**	**58**	**28**	**15**	**189**
Cord Artery pH < 7.13	0	4	1	4	0	0	9
NPV for pH < 7.13	**100.0%**	**88.9%**	**97.8%**	**93.1%**	**100.0%**	**100.0%**	**95.2%**

The outcome of the NPV analysis clearly indicates that in all participating sites, both academic and non-academic, the STAN methodology can be applied safely. It should be mentioned that the NPV assessment does not include any case with cord artery pH of <7.05.

The second primary outcome of negative percent agreement (NPA) was 90% (444/491) with a 95% confidence interval of (87.8%, 93.0%) and positive percent agreement (PPA) was 84% (31/37). Thus, NPA and PPA exceeded the 75% values set forth in the protocol. Furthermore, the overall percent agreement was 90% (475/528) with a 95% confidence interval of (87.4%, 92.5%). Therefore, the observed overall percent agreement and negative percent agreement and positive percent agreement all exceeded the 75% pre-specified value.

A number of secondary outcomes were evaluated but no quantitative thresholds of success were identified for these endpoints.

STAN Effectiveness Data

Results from the CUS demonstrate that US clinicians can appropriately use the STAN system, ST information and clinical guidelines to monitor labor and make clinical management decisions. The study demonstrated 1) the US clinicians' ability to make correct decisions to not intervene as determined by a cord artery pH level greater than 7.12 and 2) agreement of US clinicians with STAN experts on deciding whether or not to intervene (primary endpoints).

STAN Safety Data

The following Table identifies all neonatal outcomes.

	CUS	
Neonatal Outcome	**FHR+ST**	
Intention to treat. Total	n	%
including lethal malformations	530	
Apgar 1 min <4	11	2.08%
Apgar 5 min <7	6	1.13%
Apgar 5 min <4	0	
Admission to NICU	37	6.98%
Neonatal seizures	1	0.2%
Perinatal death	1	0.2%
Umbilical cord acid base data available	466	88%
Cord artery pH <7.15	27	5.09%
Cord artery metabolic acidosis	1	0.21%

There was one perinatal death related to severe cardiac malformation with hypoplastic left heart syndrome diagnosed antenatally. There was no adverse outcome that could be related to use of the STAN Fetal Heart Monitor. Two adverse events were noted during the Study, neither of which was considered device-related. No case with cord artery metabolic acidosis was unidentified. This study verified findings from the Swedish RCT that the STAN device is safe for use as a fetal heart monitor.

Conclusions and Comparison with the Swedish RCT

No significant differences were identified with regard to neonatal outcome in the CUS and SRCT studies. The following chart provides a comparison of neonatal outcomes in these two studies.

	Swedish RCT				CUS	
Neonatal Outcome	**FHR**		**FHR+ST**		**FHR+ST**	
Intention to treat. total	n	%	n	%	n	%
excluding lethal malformations	**2447**		**2519**		**530**	
Apgar 1 min <4	47	1.92	36	1.43	11	2.08
Apgar 5 min <7	28	1.14	26	1.03	6	1.13
Apgar 5 min <4	6	0.25	2	0.08	0	
Admission to NICU	181	7.40	169	6.71	37	6.98
Moderate or severe neonatal encephalopathy	8	0.33	1	0.04	0	
Perinatal death	1	0.04	2	0.08	0	
Umbilical cord acid base data available	2079	85	2159	86	466	88
Cord artery metabolic acidosis	31	1.49	15	0.69	1	0.21

Operative interventions, and induction and augmentation of labor differ between the US and Sweden, with C/Section and induction rates being higher in the US. Even with these differences, both studies have demonstrated the safe and effective use of the STAN Fetal Heart Monitor and its ability to improve the assessment of the fetal condition during labor in both Swedish and US populations.

1.10 Panel Recommendation

On April 22, 2002, a FDA Advisory Panel voted 6-5 against approving the device. The main concern of the Panel was the lack of certainty that a typical physician in the United States would achieve similar results to those seen from the Swedish data presented in the original PMA. Based on the Panel's comments and subsequent discussions with FDA, the Sponsor successfully completed additional clinical studies (the Education Study and the CUS) with physicians from the United States. These studies demonstrated that the US and Swedish experiences were comparable. (FDA to fill in the rest based on future Panel meeting.)

1.11 CDRH Decision

To be completed by FDA

1.12 Approval Specifications

To be completed by FDA