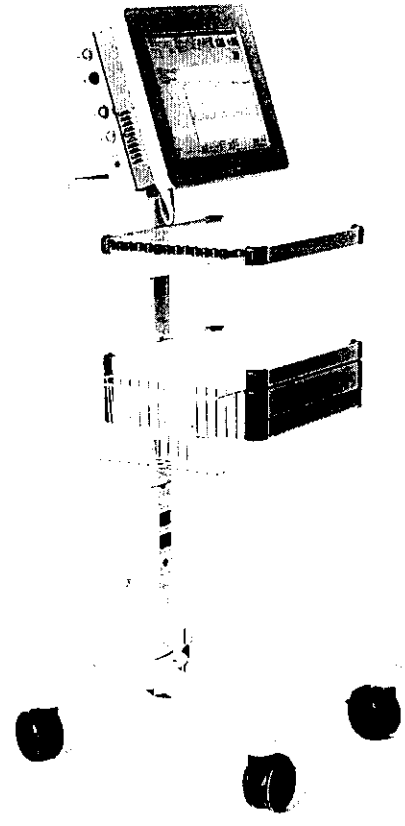
INFORMATION FOR PRESCRIBERS



STAN® S31 Fetal Heart Monitor

PRD 101 013/1 P2E, September 2005

Neoventa STAN® S31 Fetal Heart Monitor - Information for Prescribers

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DRAFT*** Information for Prescribers ***DRAFT

CAUTION: FEDERAL LAW RESTRICTS THIS DEVICE TO SALE BY OR ON THE ORDER OF A PHYSICIAN WHO HAS COMPLETED TRAINING IN THE USE OF THE DEVICE.

The user must receive specialized training in the use and interpretation of the STAN S31® Fetal Heart Monitor's Fetal ECG analysis feature to ensure proper performance and safe use of this device.

Read all instructions, including INDICATIONS, CONTRAINDICATIONS, WARNINGS and PRECAUTIONS, prior to use. Failure to follow these instructions could result in serious patient injury.

I. DEVICE DESCRIPTION

Indications for Use

The STAN S31 Fetal Heart Monitor Fetal ECG Analysis System is indicated as an adjunct to fetal heart rate monitoring to determine whether obstetrical intervention is warranted when there is increased risk of developing metabolic acidosis.

This device is intended for use in patients with:

- Planned vaginal delivery;
- >36 completed weeks gestation;
- Singleton fetus;
- Vertex presentation; and
- Ruptured amniotic membranes.

Device Components

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 fetal heart rate (FHR) are measured continuously via a scalp or spiral electrode placed on the fetal vertex and connected via a 'legplate' connecting cable to the PIB.

The legplate includes a connection for a skin electrode to be placed on 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 (tocodynamometer or 'TOCO') placed on the abdomen of the mother or by an intrauterine pressure catheter (IUPC) 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. **A spiral electrode is needed whenever FECG is to be recorded.**

The TOCO, IUPC, ultrasound transducer and spiral electrodes must be purchased separately from the STAN System. The STAN S31 is designed for use with commercially available disposable single-spiral electrodes that are compatible with STAN S31.

CAUTION: Use of other electrodes may cause, the ECG signal from the scalp electrode to be of insufficient quality and result in a poor quality recording.

General Technical Description and Principle of Operation of the STAN System

The STAN 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 with 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 ('T/QRS 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 should be taken clinically in relation to FHR changes and ST-events.

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; and
- The DSP Software running on the Digital Signal Processor on the DSP Board in the PIB which handles digital filtering.

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

Using fetal ECG information, the STAN S31 fetal heart monitor calculates and displays a ratio of the amplitude of the T wave and QRS complex of the fetal ECG ('T/QRS'), and also calculates the incidence of abnormal "biphasic" ST waveforms. T/QRS ratio changes are constantly monitored and a message is printed in the event of a significant increase **over time.**

The STAN algorithms use two signal characteristics derived from the FECG to determine events: ST segment slope differences and T/QRS amplitude differences. The algorithms generally operate by comparing the latest sample (either an ST segment or a T/QRS value) to an established baseline to see if there is a change.

The STAN system calculates an average ECG waveform from the FECG channel (scalp-to-skin lead). Every fetal heartbeat generates an FECG complex, which is assessed by STAN® S31 against strict quality criteria. The FECG complexes satisfying the quality criteria qualify for the subsequent analysis. The averaging is performed over 30 consecutive qualified FECG complexes. The device uses the average ECG waveform to process the T/QRS ratios - the ratio between the T-wave amplitude and the QRS-complex amplitude. A T/QRS baseline is computed every minute and monitored for multiple characteristics, contributing to a determination of a T/QRS difference and the identification of a significant event. The initial 20 minutes are used to collect T/QRS baseline data to allow for a robust determination of starting values used by the processing algorithms for event detection.

The ST analysis software conditions and analyzes the raw ECG signal to identify additional characteristic parameters of the T wave and QRS complex used in decision making. The decision algorithm evaluates these parameters looking for the 3 types of events: episodic T/QRS rise, baseline T/QRS rise, and biphasic ST. Biphasic is a term that indicates that the slope of the ST segment has become negative, which the decision algorithm uses as an indicator of fetal abnormality. Biphasic events are further classified into category 1, 2, or 3 indicating that the slope is above baseline, crossing the baseline, or below baseline, respectively.

At start up the system calculates a baseline to detect T/QRS rises. This can take a maximum of 20 minutes. During this time it is possible that the system does not register all ST-events. The device indicates when the signal quality is poor or when breech mode is activated. When the signal quality is poor the device may not register an event. Signal quality, as with internal FHR monitoring is dependent on the sensor making good contact with the fetal scalp.

There are 2 modes of clinical operation:

- Recording Mode - used to record data
- Signal Mode - used to check fetal ECG signal quality

A Review Mode is used to review previously recorded data while recording. A Demonstration Mode is available for simulating a patient recording.

II. INDICATIONS, CONTRAINDICATIONS, WARNINGS, PRECAUTIONS, AND SIGNAL QUALITY

A. Indications for Use

The STAN S31 Fetal Heart Monitor Fetal ECG Analysis System is indicated as an adjunct to fetal heart rate monitoring to determine whether obstetrical intervention is warranted when there is increased risk of developing metabolic acidosis.

This device is intended for use in patients with:

- Planned vaginal delivery;
- >36 completed weeks gestation;
- Singleton fetus;
- Vertex presentation; and
- Ruptured amniotic membranes.

B. Contraindications

Use of the STAN S31 fetal ECG analysis function is contraindicated in the following situations:

- Non-reassuring, Grade 2 Fetal Heart Rate classification (as defined in the STAN S31 Training Materials). When fetal asphyxia has been severe and long lasting, the ST waveform returns towards normal, reflecting a markedly reduced ability by the fetus to respond. **A change over time can not be expected, therefore reliance on ST event signals in this situation may lead to serious adverse neonatal outcome.**
- In patients for whom use of a fetal scalp electrode is contraindicated such as:
  - HIV
  - Infectious hepatitis
  - Active herpes simplex virus
  - Known or suspected fetal coagulation disorder
- Patients with fetal bleeding disorders. Chronic fetal bleeding (eg. due to partial placental abruption) leading to loss of fetal blood volume may result in a reduction in the margin of safety or time that the fetus can successfully respond to hypoxia.

- Monitoring initiated in the second stage of labor, since time may be insufficient to establish the baseline fetal ECG data required for automatic ST event signals.
- Patients experiencing precipitous labor, as rapid labor may preclude acquisition of necessary baseline fetal ECG data.
- Patients receiving Transcutaneous Electrical Nerve Stimulation (TENS) for analgesia during labor because TENS may interfere with acquisition of the fetal ECG signal.
- Patients requiring immediate delivery as in the following situations:
  - Conditions that preclude vaginal delivery such as documented or suspected placenta previa
  - Cord prolapse
  - Need for immediate delivery unrelated to fetal heart rate or fetal ECG, such as active maternal or fetal bleeding.

C. Warnings

Warnings in this manual are identified by the WARNING symbol shown below.

A warning alerts you to potentially serious outcomes (death, injury, or adverse events) to the user or the patients.

- **WARNING:** Intrapartum management of the fetus is a complex process that uses a variety of maternal and fetal considerations in the formulation of clinical decisions. The STAN Training Program and Guidelines are recommendations that are based on extensive clinical investigation and subsequent prospective clinical use. STAN Training Program and Guidelines are not a substitute for individualized clinical assessment and decision-making for each patient.

- **WARNING:** ST analysis is only an adjunct to fetal heart rate monitoring and should never be used exclusively to make patient management decisions. There are situations in which the fetus is experiencing hypoxia but an automatic ST event signal may not appear. These include the following:
  - Inadequate time to obtain baseline ECG
  - Poor signal quality
  - Pre-existing hypoxia

  If there is reason to believe that any of the above apply, clinical decision making should not include ST analysis.

- **WARNING:** Centralized Monitoring Systems connected to STAN can display EFM tracings for FHR and uterine activity but may not support the display of Fetal ECG analysis information (ST analysis data). In this case ST information including events and signal quality information will not be available on the Centralized Monitoring System. Failure to regularly check the STAN monitor and Event Log for important

ST information directly, especially during periods of non-reassuring fetal heart rate, may lead to important information being missed and injury to the patient.

- **WARNING:** Do not rely solely on the appearance of an ST event marker to signal the need for obstetrical intervention. If you suspect, on the basis of FHR-only and/or clinical data that the fetus is experiencing severe hypoxia, you should manage the patient accordingly despite the absence of an ST event marker.

- **WARNING:** If the fetal ECG analysis capability is lost, manual interpretation of ECG/ST data should not be attempted. Clinical management should be based on available data, e.g. FHR.

- **WARNING:** When fetal ECG analysis has not been available for ≥4 minutes and efforts to readjust the monitor fail to restore the signal. Clinical management should be based on available data, e.g., FHR. No inferences regarding fetal status should be made on the basis of earlier fetal ECG analysis.

- **WARNING:** At the start of a recording, special attention should be paid to the log, and visual inspection of the FECG signal. If a "Poor FECG Signal Quality" event is active in the Event Log, adequate measures should be taken to improve the signal quality (by re-applying the electrodes if necessary).

- **WARNING:** Fetal ECG is similar to, but not the same as Adult ECG. Fetal heart pathology, such as hypoplastic left ventricle, can not be diagnosed from the fetal ECG signal. Even if the fetal ECG pattern appears normal, it can not be assumed that the fetal heart is normal. STAN S31 is not a substitute for a fetal echocardiography exam.

- **WARNING:** Before using STAN S31 output, verify that the ECG complex is of a normal appearance, by observing the raw ECG-signal in Signal Mode. In the event of a constant, non-fluctuating fetal heart rate, ensure that no other device is interfering with the STAN S31 signal.

- **WARNING:** The STAN S31 displays an inverted ECG waveform pattern (negative P waves) when the STAN S31 is applied on fetuses in breech presentation. If an inverted ECG is observed, fetal presentation and correct placement of the scalp electrode should be reassessed.

- **WARNING:** If insufficient monitoring time has accrued, STAN may be registering T/QRS signals but may not be ready to automatically signal ST events. In this situation, it may be possible to manually/visually detect a rise in T/QRS before an automatic ST event appears on the screen. For example, a prolonged bradycardia may occur with an accompanying rise in T/QRS before an ST event appears. In such situations, you should treat the observed T/QRS rise as a significant event in making patient management decisions.

- **WARNING:** Locate the monitor near the patient in a position that ensures it cannot accidentally fall on to the patient. Failure to do so could result in patient injury.

- **WARNING:** The STAN S31 fetal heart monitor is not shielded against electrocautery equipment or defibrillators and must not be used together with or in proximity to flammable substances, e.g. anaesthetic gases.

- **WARNING:** STAN S31 should be used only in rooms that are relatively free of dust, moisture, vibrations and extreme temperatures.

- **WARNING:** Neoventa Medical guarantees the functioning of the device only if it is used within the temperature range 50-104 degrees F.

- **WARNING:** Moisture - Ensure that the equipment and all its cables are dry when used. Condensation may occur if it is moved from one building to another. Should this be the case, dry the equipment thoroughly prior to mains connection.

- **WARNING:** The STAN S31 should not be used to monitor patients during water births, in whirlpool or submersion water baths, during showers, or in any other situation where the mother is immersed in water. Doing so may result in electrical shock hazard.

- **WARNING:** Radio transmission equipment, mobile telephones, magnetic resonance imaging (MRI) machines etc. may affect the functioning of the device and must not be used in its proximity. Particular care must be observed during the use of strong emission sources such as electrocautery, to prevent electrocautery cables etc. being laid over or near the device.

D. Precautions

Precautions in this manual are identified by the CAUTION symbol shown below.

A caution alerts you to exercise care necessary for the safty and effective use of the STAN S31 system.

- **CAUTION:** Signal quality must be continuously evaluated in order to use the fetal ECG as an adjunct to fetal heart rate in clinical management. Signal quality problems should be suspected in the following situations:
  - Signal information window reads "ST disabled"
  - Event log reads "Poor FECG signal quality"
  - Difficult to see QRS complex
  - Signal bar shows level 2 or less

  In the event of signal quality problems, the following corrective action should be taken:
  - Check skin electrode
  - Check scalp electrode
  - Check legplate cable

  See section below for further information regarding signal quality.

- **CAUTION:** The safety and effectiveness of the STAN S31 System has not been systematically evaluated in the following situations:
  - Immature fetus (less than 36 gestational weeks)
  - Twin gestation

- Breech presentation

However STAN S31 is capable of monitoring breech and twin gestations, so if you do chose to use the device in this/these situations you should take note of the following:

- Breech Presentation: attachment of a spiral fetal scalp electrode to breech will result in an inverted fetal ECG pattern. The STAN monitor is equipped with a "breech mode" function that should be initiated in the event that there is a clear indication for attempted vaginal breech delivery by a clinician with requisite skills.
- Twin Gestation: in the case of twins, the spiral electrode can only be applied to Twin A, thus fetal ECG data will only be available for that twin. Twin B can be monitored exclusively with external Doppler transducer using the STAN system. The STAN Clinical Guidelines, which are based on fetal heart rate plus ST data analysis, can only be applied to Twin A in the case of twins. Clinical management decisions regarding Twin B can not be based on STAN Guidelines because ECG analysis is not available.

- **CAUTION:** The STAN S31 ECG analysis feature is only an adjunct to conventional fetal heart monitoring, and should not be used as a substitute for clinical interpretation of FHR.

- **CAUTION:** All Instructions for Use, Contraindications, Warnings and Precautions for the use of the fetal scalp electrode should be observed.

- **CAUTION:** The STAN S31 should not be used if amniotic membranes have not fully receded away from where the scalp electrode has been applied. Contact between the electrode and membrane fragments could result in erroneous fetal ECG measurements.

- **CAUTION:** Do not attempt to rupture amniotic membranes with the scalp electrode. Doing so may result in erroneous fetal ECG measurements.

- **CAUTION:** Take care that the cables of the STAN S31 are not damaged during use or storage. Transducers and other connectors may be damaged if stepped on. When connecting cables and transducers, make sure there is no risk of anyone stumbling or tripping over the cables, since the patient and fetus may be injured if the scalp electrode or skin electrodes are pulled off. Connect only the mains cable to the mains supply.

- **CAUTION:** Do not use STAN S31 if the outside monitor cover appears to be damaged. Doing so may result in patient injury and instrument malfunction.

- **CAUTION:** Do not remove the outside monitor cover. Doing so may result in electrical shock hazard. There are no user-serviceable parts inside.

E. Electrical safety precautions

- **CAUTION:** Avoid contact between the scalp electrode, skin electrode or legplate contacts and earth or any electrically conductive object.

- **CAUTION:** Power source - The STAN S31 fetal heart monitor must be used only with a power source of 100V/60 Hz. The mains cable has three conductors for connection to an earthed wall socket. The system must be connected to an outlet with proper protective earth wiring.
- **CAUTION:** Incorrect mains connection - Check that the equipment is not connected to the mains by any component other than mains cable or approved trolley.
- **CAUTION:** Earth connection - The STAN S31 fetal heart monitor must have a protective earth connection. All forms of earth leakage represent a potential safety risk that may seriously injure patient and operator.
- **CAUTION:** System combinations - The electrical devices that may be connected to STAN S31 (Maternal Vital Signs Monitor, Thermal Recorder, network interface adapter and Central Monitoring Systems through the serial port isolation adapter) are described in the STAN S31 User Manual. If other medical electrical devices are connected to the patient, these devices should be powered from separate power outlets, and not from multiple socket outlets, to ensure the highest level of electrical safety. Contact a qualified technician or the supplier for more information.

F. Importance of signal quality

Signal quality may deteriorate for a short period of time due to the electrical noise introduced by active movements of the mother. Short-time loss of ST-information may also be caused by maneuvers involving the area where the scalp electrode is applied, such as vaginal examinations or fetal scalp blood sampling. Usually, in such situations, the signal quality and the ST-information will recover spontaneously. A "Poor FECG signal quality" event will be recorded in the Event log if no ST-datapoint has been plotted for more than 90 seconds. If the signal quality does not recover spontaneously, the following corrective action should be taken.

- Inspect the FECG signal window and make sure a "Fetal ECG" is what is recorded. Observe appearance of the complexes, amplitude, and level of noise.
- Make sure the **skin** electrode is properly applied: **skin** prepared as recommended, **skin** electrode is well-attached and not placed directly over skeletal muscle. A poorly attached **skin** electrode will increase susceptibility to electrical noise
- If necessary change the **scalp** electrode. A loose **scalp** electrode usually causes low amplitude FECG complexes and poor signal quality

Recommendations for addressing suspected poor signal quality:

- **If the FHR is reassuring and**
  - signal quality recovers, continue STAN monitoring according to guidelines

- signal quality doesn't recover and the ST data continues to be missing, it is the individual clinician's decision for how long signal recovery attempts should continue. If signal doesn't recover and FHR becomes non-reassuring, please see below.

- **If the FHR is non-reassuring grade 1 and**
  - signal quality improves immediately with no ST-gaps longer than 4 minutes, continue STAN monitoring according to the guidelines
  - signal quality can not be re-established and the ST information is not satisfactory, base the clinical decision on FHR data.
- **If FHR is non-reassuring grade 2 (preterminal)**
  - immediate intervention is indicated

III. ADVERSE EVENTS

The device was evaluated in a prospective, randomized, controlled clinical trial of nearly 5000 patients (Swedish Randomized Controlled Trial or SRCT). There were 29 adverse outcomes in that study:

- Peripartum death (3)
- mild/moderate/severe encephalopathy, with or without metabolic acidosis (11)
- neonates admitted to Special Care Baby Unit (SCBU) with metabolic acidosis and other symptoms (15)

There is only partial overlap between the above cases and the total number of cases in the study in which metabolic acidosis was documented (46). The incomplete overlap is explained by the fact that some of the infants with umbilical cord metabolic acidosis were clinically perfectly normal, vigorous neonates with high Apgar scores. These infants were not included in the count of "adverse outcomes." Alternately, some infants with normal cord blood or unavailable cord blood showed evidence of intrauterine hypoxia and/or asphyxia. These made it into the category of "adverse outcomes."

	Study Arm FHR-only	Study Arm FHR + ST
Death (intrapartum)	1	2
Severe Encephalopathy	3	0
Moderate Encephalopathy	4	0
Mild Encephalopathy	1	3
SCBU Admissions	10	5

Table 1. Adverse Events

Of the 3 peripartum deaths in the study, 2 were in the FHR + ST arm and 1 was in the FHR only arm, and the difference between the two arms was not statistically significant. There were no cases of moderate or severe encephalopathy in the FHR + ST arm. Of the 15 babies admitted to the SCBU with metabolic acidosis and "other symptoms" not neurologic in nature (e.g., respiratory problems), all were discharged in good condition without evidence of sequelae.

The device was also evaluated in two trials in the United States. The first of these trials was intended to test the training program and did not involve any patients. The second trial was intended to study use of the device for clinical management of patients in the United States.

In this second study, 530 patients were enrolled. The protocol called for a case based analysis of all cases with cord artery pH<7.15. Of these 27 cases, there was one case of metabolic acidosis (pH 6.88, BDecf 14.4 mmol/L) but this infant had Apgar score of 7 an 8 at 1 and 5 minutes respectively, and was not one of the 8 infants admitted to the NICU.

One case had a poor outcome during the neonatal period. Of 4 cases with pH of ≤7.05, one infant (pH 7.05, BDecf 10.3mmol/L, Apgars 6 and 8) was admitted to the NICU for observation due to grunting, maternal fever and possible sepsis. At 28 hours of age, the infant displayed seizure activity lasting for 1 minute. The initial EEG was abnormal. MRI two days later showed "acute infarction involving left anterior brain stem and basal gan-

glia + portions of left frontal and temporal lobe." The site considered this adverse event to be non-device related.

There was an important protocol deviation in that this subject had a private physician (not an investigator) who attended the labor. The study investigator obtained informed consent from the patient and placed the STAN system, but then left the room. Labor and delivery proceeded under the management of the private physician.

The one death was an infant that was diagnosed in utero at approximately 28 weeks of gestation with a hypoplastic left ventricle. The infant died at approximately two weeks post partum during corrective surgery. This death was determined to be unrelated to the use of the STAN S31 device.

IV. CLINICAL STUDIES ON THE SAFETY AND EFFECTIVENESS OF THE STAN SYSTEM

A. Overview

A number of clinical studies of the STAN system have been conducted since the mid-late 1980's. These studies can be divided into 3 types: (1) Observational Studies, (2) Randomized Interventional Studies, and (3) US Bridging Studies.

The Observational Studies are varied. Eearly observational studies evaluated how well fetal ECG data corresponded to events in labor and potential diagnostic performance of the STAN System. Later observational studies evaluated how well retrospective review of tracings by clinicians blinded to outcome could "predict" fetal compromise (Luzietti et al, 1999 and Amer-Wahlin I, Bordahl P et al, 2002). In addition, following the Swedish RCT, the Gothenburg Study was initiated. It was a prospective, open label, general use, interventional study that evaluated how the neonatal outcome has changed with time, with the increase use of STAN in the clinic (unpublished).

The randomized interventional studies were conducted to evaluate the impact of the ST analysis on the rate of metabolic acidosis. There were two such studies, the Plymouth Study (Westgate et al, 1993) and the Swedish RCT (Amer-Wahlin, Hellsten et al, 2001). The Swedish RCT is the pivotal clinical trial that demonstrated the safety and effectiveness of the STAN S31. Five thousand women in labor were randomized to be monitored with conventional FHR or with FHR plus ST data.

The US Bridging Studies were conducted to evaluate the transferability of the STAN technology to US obstetrical wards. The first US Study was the Education Study which examined how well US clinicians learned STAN principles. The second US Bridging Study was the Clinical Use Study, a non-randomized observational study that evaluated two types of endpoint: (1) correctness of clinical decisions not to intervene in cases with non-reassuring fetal heart tracing was evaluated based on cord artery pH; and (2) level agreement between US clinicians and STAN experts (who were reviewing tracings retrospectively) on the need to intervene.

References

Observational Studies

Arulkumaran S, Lilja H, Lindecrantz K, et al. Fetal ECG waveform analysis should improve fetal surveillance in labour. J Perinat Med 1990;18(1):13-22.

Maclachlan NA, Spencer JAD, Harding K, Arulkumaran S. Fetal acidemia, the cardiotocograph and the T/QRS ratio of the fetal ECG during labor. Br J Obstet Gynaecol 1992;99(1):25-31.

Murphy KW, Russel U, Johnson P, Valente J. Clinical assessment of fetal electrocardiogram monitoring in labor. Br J Obstet Gynaecol 1992;99(1):22-37.

Luzietti R, Erkkola R, Hasbargen U, et al. European Community Multicenter Trial "Fetal ECG Analysis During Labor": ST plus CTG Analysis. J Perinat Med 1999;27:431-440.

Amer-Wahlin I, Bordahl P, Eikeland T, et al. ST analysis of the fetal electrocardiogram during labor: Nordic observational multicenter study. J Matern Fetal Neonatal Med 2002;12:260-266.

Dervaitis KL, Poole M, Schmidt G, et al. ST segment analysis of the fetal echocardiogram plus electronic fetal heart rate monitoring in labor and its relationship to umbilical cord arterial blood gases. Am J Obstet Gynecol 2004;191:879-884.

Kwee A, van der Hoorn-van den Beld CW, Veerman J, et al. STAN S21 fetal heart monitor for surveillance during labor: an observational study in 637 patients. J Matern Fet Neonatal Med 2004;15:400-407.

Luttkus AK, Noren H, Stupin JH, Blad S, et al. Fetal scalp pH and ST analysis of the fetal ECG as an adjunct to CTG - A multicenter, observational study. J Perinat Med 2004;32:486-494.

Randomized, Interventional Studies

Westgate J, Harris M, Curnow JS, Greene KR. Plymouth randomized trial of cardiotocography only versus ST waveform plus cardiotocogram for intrapartum monitoring in 2400 cases. Am J Obstet Gynecol 1993:169:1151-1160.

Amer-Wahlin I, Hellsten C, Noren H et al. Cardiotocography only versus cardiotocography plus ST analysis of fetal electrocardiogram for intrapartum fetal monitoring: a Swedish randomized controlled trial. Lancet 2001;358:534-538.

Noren H, Amer-Wahlin I, Hagberg H et al. Fetal electrocardiography in labor and neonatal outcome: data from the Swedish randomized controlled trial on intrapartum fetal monitoring. Am J Obstet Gynecol. 2003;188:183-92.

US Bridging Studies

(unpublished)

B. Nordic Study on Diagnostic Performance of Fetal ST Analysis - Clinical Accuracy

Study Objective

Neoventa conducted an observational, non-randomized, non-interventional study (Amer-Wahlin, Bordahl et al., 2002) to determine the clinical accuracy of the STAN fetal Heart Monitor, examining clinical outcome when ST analysis was added to conventional intrapartum fetal monitoring. The objective of the study was to examine diagnostic power of FHR plus ST analysis to identify adverse labor outcomes such as neurological symptoms and/or metabolic acidosis.

The reason that this study is so significant and is being emphasized is that this study was the only study that was both non-interventional and contained an adequate number of metabolic acidosis cases to estimate sensitivity and specificity.

Study Endpoints

Endpoints included operative delivery and intervention rates and the accuracy measures of sensitivity, specificity, positive predictive value, and negative predictive value. To determine the accuracy measures, a case was defined as warranting intervention if the case was exposed to intrapartum hypoxia or asphyxia based on neurological symptoms and/or cord artery metabolic acidosis (CA pH < 7.05 and BDecf > 12 mmol/L).

Study Hypothesis

None

Study Methodology

This multi-center observational study was conducted between 1998-99 at 12 labor wards (8 Norwegian, 4 Swedish) and included a total of 573 women in labor. This period overlaps the conduct of the SRCT (December 1998 to June 2000). The study used a prototype of STAN S21 called the STAN ESST, which included an algorithm that automatically identified ST events. Three of the Norwegian departments had previous experience with the old STAN 8801 unit.

The investigators were instructed to manage labor cases on the basis of CTG information alone. ST information was also available, but the investigators were instructed only to check its signal quality and operation of the recorders. Afterwards, one clinical reviewer evaluated the [FHR + ST] tracings blinded to outcome and grouped them either into an intervention category or a non-intervention category according to previously developed STAN guidelines. This determination was made by visual inspection and by using a computerized algorithm.

Study Results

Fifteen infants were diagnosed as having been exposed to intrapartum hypoxia or asphyxia based on neurological symptoms and/or metabolic acidosis. The sensitivity of [FHR + ST] clinical guidelines to recommend intervention in these cases was 100% (15/15). The specificity of the guidelines was 95% (530/558). The positive and negative predictive values (PPV and NPV) were 35% (15/43) and 100% (530/530). Also of interest in this study was that the projected rate of operative interventions, if intervention had been taken according to [FHR + ST] guidelines, would have been only 7.5%, compared to the actual rate of 15.3%.

Reference

"Amer-Wahlin I, Bordahl P, Eikeland T, et al. ST analysis of the fetal electrocardiogram during labor: Nordic observational multicenter study. J Matern Fetal Neonatal Med 2002;12:260-6."

C. Swedish Randomized Controlled Trial (SRCT)

Study Objective

Primary objective:
To reduce perinatal morbidity as identified by a significant cord artery metabolic acidosis (pH<7.05 and BDecf >12.0 mmol/L).

Secondary objectives:

- to evaluate the use of FHR and ST waveform protocols and guidelines in clinical practice; and
- to reduce operative interventions

Study Hypothesis

Primary Hypothesis:
Intrapartum monitoring with Electronic Fetal Monitoring (EFM) combined with ST waveform analysis will result in an improved perinatal outcome as compared with EFM alone.

The statistical hypothesis was that there would be at least a 50% reduction in the number of cases with metabolic acidosis, with a power of 80% and a test performed on the 5% level.

Other study endpoints were:

- change in neonatal morbidity as identified by Apgar scores at 5 minutes, admission to special care baby unit, and neonatal seizures or other neurological abnormalities;
- change in frequency of operative delivery;

Study Methodology

The study was conducted at three university-based labor wards in Sweden. The STAN system was used in both arms of the study. In the STAN arm, clinicians used T/QRS event data and ST segment analysis adjunctively with FHR tracing to manage patients according to STAN clinical guidelines. In the control arm of the study, the only data from the scalp electrode that was available to the clinician was continuous fetal heart rate tracing.

For all subjects, both umbilical cord arterial and venous blood were to be sampled according to the following strict guidelines: The cord was to be double-clamped as soon as possible after birth of the baby (before the placenta was delivered) and using pre-heparinized syringes or capillary tubes the blood was to be obtained from both an artery and the vein. An alternative acceptable procedure was to puncture both vessels directly at delivery.

Inclusion Criteria

- >36 completed gestational weeks
- in cephalic presentation
- in active labor
- intrapartum monitoring with fetal scalp electrode

Exclusion Criteria

- recording time during first stage of labor <30 minutes
- recording only represents second stage of labor
- lag time between end of recording and delivery exceeds 20 minutes
- trans-cutaneous nerve-stimulation (TENS) for analgesia

- gross fetal abnormality diagnosed prior to labor

Management Guidelines

In the control arm of the study, subjects were managed according to standard FHR-based practice. The sponsor prepared a chart describing possible fetal heart rate patterns during the first and second stages of labor, and a recommended action for the clinician to take depending on the stage of labor and the heart rate pattern. The definitions of fetal heart rate patterns for this chart were based on terminology proposed by the International Federation of Gynecology and Obstetrics (FIGO) (Int. J. Gynaecol. Obstet., 1987, 25:159-167).

A set of clinical guidelines were developed, to be used in the [FHR + ST] arm of the study. The most significant aspect of the STAN clinical guidelines is that they recommend clinical intervention on the basis of both the ECG event data and FHR pattern. These guidelines were developed further to become the current Classification of FHR Patterns and STAN® Simplified Clinical Guidelines included as part of the labeling package for this device.

Patient Population

The SRCT took place between December 1, 1998 and June 4, 2000. Three university-based hospital labor wards contributed approximately equally to the total number of patients in this trial: University Hospital Lund (36%); University Hospital Malmo (31%); and Sahlgrenska University Hospital, Gothenburg (33%).

Patient accounting for the SRCT is summarized in the patient tree in Figure 1. The total number of subjects treated was 4966. The FHR + ST arm enrolled 2519, and the FHR-only arm enrolled 2447. Neoventa Medical evaluated the two main clinical endpoints for this population, and referred to it as Analysis I. (The "Analysis II" will be explained below.)

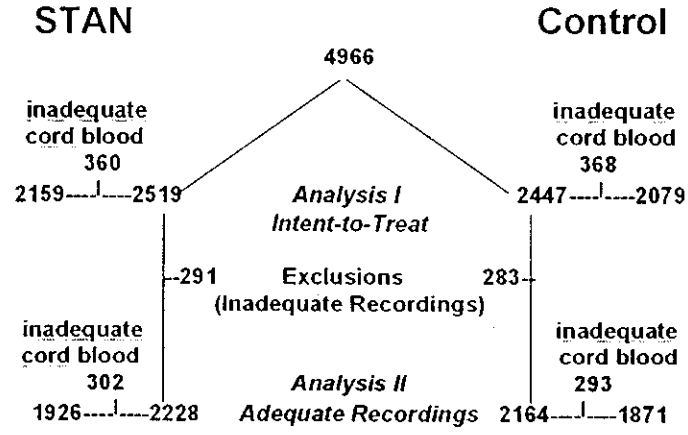


Figure 1. Swedish RCT Patient Tree

Interim Analysis

The study protocol called for an interim analysis of the data after treatment of 1600 subjects to assess the true incidence of metabolic acidosis in the study population and whether 3200 cases was sufficient to demonstrate a 70% reduction in the number of newborns with cord artery metabolic acidosis, assuming an incidence of 1.3%, $\beta = 0.20$ and $\alpha = 0.05$. At interim analysis, the actual incidence turned out to be 0.65%. The results for the two arms were not blinded to Neoventa. Therefore, a second power analysis was done to calculate the number of additional cases needed. The number of additional cases was 2160. A new study deadline was set on the basis of the previous rate of recruitment.

A second result of the interim analysis was that Neoventa Medical decided to retrain clinicians in how to use the STAN system. This came about because of protocol violations that occurred during the first 1600 cases. The study results were then presented for "before retraining" (n=2583) and "after retraining" (n=2383). Because the decision to retrain came well after the planned interim analysis of the first 1600 cases, the number of subjects treated before retraining does not correspond to 1600.

Effectiveness Evaluation

For the "intent-to-treat" population (Table 2), there were 31/2079 (1.5%) cases of metabolic acidosis in the FHR-only arm and 15/2159 (0.7%) of cases in the [FHR + ST] arm (p=0.02). Therefore, there was a statistically significant reduction in cases of metabolic acidosis in the patients monitored with the STAN S21. The reason that the denominator numbers in these fractions are different from the actual numbers of subjects randomized in each arm is that 368 subjects in the control arm and 360 subjects in the STAN arm did not have adequate cord blood data. For example, blood was not sampled from both an umbilical artery and the umbilical vein or there was evidence from the blood gas values that cord clamping had occurred too late for the samples to be representative of true fetal hypoxic status in utero.

A secondary endpoint was operative deliveries for fetal distress (ODFD), a category that includes instrumented vaginal deliveries including high forceps as well as cesarean section. For the intent-to-treat population, the rate was 227/2447 (9.3%) for the FHR-only arm and 193/2519 (7.7%) for the [FHR + ST] arm (p=0.047). This difference was statistically significant, in favor of the STAN system.

The rate for cesarean section for fetal distress (CSFD) in the intent-to-treat population was 97/2447 (4.0%) in the FHR-only arm and 87/2519 (3.5%) in the [FHR + ST] arm (p=0.38). This difference was not statistically significant.

	FHR	FHR + ST
Cases of metabolic acidosis (p=0.02)	31/2079 (1.5%)	15/2159 (0.7%)
Total ODFD (p=0.047)	227/2447 (9.3%)	193/2519 (7.7%)
CSFD (p=0.38)	97/2447 (4.0%)	87/2519 (3.5%)
Apgar 1 min < 4	47/2447 (1.92%)	36/2519 (1.43%)
Apgar 5 min < 7	28/2447 (1.14%)	26/2519 (1.03%)

	FHR	FHR + ST
Admission to SCBU	181/2447 (7.40%)	169/2519 (6.71%)
Moderate or severe neonatal encephalopathy	8/2447 (0.33%)	1/2519 (0.04%)
Perinatal death	1/2519 (0.04%)	2/2519 (0.08%)

Table 2. Results, Intent to Treat (Analysis I)

"Inadequate Recordings"

Neoventa Medical performed an additional analysis of the clinical study endpoints (Analysis II) after excluding 291 cases from the [FHR + ST] arm and excluding 283 cases from the FHR-only arm. (Refer again to "patient tree" above.) Patients in both arms were excluded for inadequate recordings when the following criteria were met:

- less than 20 minutes of data collected with the fetal scalp electrode (37.5%)
- more than 20 minutes elapsed between removal of scalp electrode and delivery (56.1%);
- congenital malformations (1.3%); or
- "other" (5.1%)

Therefore, 93.6% of the "inadequate recordings" were related to duration of the tracing with respect to setting ECG baseline, assessing FHR and ST patterns and to time of delivery. These tracings did not meet the standards set to enable optimal assessment of either FHR or ST information. However, they are not necessarily synonymous with "signal quality" problems.

For Analysis II, (Table 3) there was a statistically significant decrease in cases of metabolic acidosis in the [FHR + ST] arm. Also, the "p" value for the metabolic acidosis endpoint implies greater statistical significance for Analysis II than for Analysis I.

The results for Analysis II for the endpoint ODFD also reinforced the finding from Analysis I that there was a statistically significant reduction in ODFD in subjects monitored with [FHR + ST] compared with FHR-only. Again, the statistical significance of this finding improved in Analysis II.

For CSFD, in Analysis II the trend towards reduction in the [FHR + ST] arm became statistically significant (p=0.04).

	FHR	FHR + ST
Cases of metabolic acidosis (p=0.01)	27/1871 (1.44%)	11/1926 (0.57%)
Total ODFD (p=0.009)	173/2164 (7.99%)	132/2228 (5.92%)
CSFD (p=0.04)	63/2164 (2.91%)	43/2228 (1.93%)
Apgar 1 min < 4	38/2164 (1.76%)	23/2228 (1.03%)
Apgar 5 min < 7	21/2164 (0.97%)	17/2228 (0.76%)
Admission to SCBU	151/2164 (6.98%)	132/2228 (5.92%)
Moderate or severe neonatal encephalopathy	7/2164 (0.32%)	0/2228 (0.00%)
Perinatal death	0/2164 (0.00%)	0/2228 (0.00%)

Table 3. Results, Adequate Recordings (Analysis II)

D. United States "Bridging Studies"

1. Education Study

Study Objective

The objective of the study was to evaluate the ability of US obstetrical staff, who are experienced in the application and interpretation of standard intrapartum electronic fetal heart rate (FHR) monitoring, to understand and apply the STAN concept of fetal ECG analysis.

Study Methodology

This was a "virtual" clinical study which consisted of 13 US clinicians acting as raters to evaluate a library of 51 tracings from European patients whose labors were monitored with the STAN S21. This library of cases was selected on the basis of the cord artery pH values in order to challenge clinicians with a range of pathology. All of these cases had previously been evaluated in a similar fashion by Swedish clinicians considered experts in the use of the STAN monitor. The distribution of cases stratified by pH was as follows:

- pH <7.05 (9 cases)
- pH 7.05-7.14 (10 cases)
- pH ≥7.15 (32 cases)

The tracings were presented for evaluation 3 times. Each time, the cases were presented in a random order. The 1st exam was before training on STAN and consisted of FHR-only. The 2nd was after completion of training on STAN which includes training in fetal heart rate tracings, but raters used FHR-only again. The 3rd exam immediately followed the 2nd exam for that case but allowed raters to use FHR+ST. For each case, the US investigator was to indicate whether or not an intervention was needed, and if so, the time at which the tracing indicated an intervention.

A panel of seven European clinicians, considered by the sponsor to be experts in FHR+ST analysis, had previously examined the same group of 51 tracings blinded to the pH data. Agreement of the US raters with the Swedish experts is an aspect of some secondary hypotheses of the study.

Study Hypotheses

Primary Hypothesis

The mean % agreement with true intervention status among the US raters would be statistically significantly greater for Exam 3 (FHR+ST) than Exam 2 (training completed, FHR-only allowed). That is, on average, US raters are more likely to make the correct decision using FHR+ST than using FHR-only.

Secondary Hypotheses

There were several secondary hypotheses. An important hypothesis was that the mean absolute difference between the Swedish experts and the US raters in the median time of intervention will be less than 20 minutes.

There was no numerical "threshold" for success. The primary and secondary hypotheses were defined to be demonstrated if there was a statistically significant difference between the two groups being studied.

Training for US Education Study

The STAN simplified clinical guidelines were modified prior to this study to reflect US terminology, according to the National Institute of Child Health and Human Development (NICHHD) guidelines (NICHHD Research Planning Workshop "Electronic Fetal Heart Rate Monitoring: Research Guidelines for Interpretation", American Journal of Obstetrics and Gynaecology, 1997, Vol 177, Nr. 6, p.1385-1390). Additionally, the strip chart print speed was modified for the US raters to be consistent with US standards. Otherwise, the US participants received the same training and took the same certification test as described in Section VI on STAN Training. (The "Credentialing" program had not been instituted at the time of the US Education Study.)

Primary Hypothesis Effectiveness Evaluation

Three of the 13 raters were not certified (i.e. did not pass the certification exam on the first attempt by the score of 16/18 required to pass) but still rated the tracings during exams 2 and 3. Analyses were made excluding as well as including these three raters.

For the US investigators, the mean percent agreement with true intervention status (average consensus) was 47% for Exam 1 (FHR-only, before training), 53% for Exam 2 (FHR-only, after training), and 69% for Exam 3 (FHR+ST, after training) (Table 4). From a repeated measures analysis, the difference in mean % agreement between Exams 3 and 2 was statistically significant ($p = 0.0001$). The small p value and positive difference indicates that the primary hypothesis that the mean % agreement would increase from Exam 2 to Exam 3 was met.

As a benchmark for comparison, the European experts as a group improved from 59% mean % agreement when reading with FHR-only to 85% when reading with FHR+ST (Table 4).

	FHR-only, before training		FHR-only, after training		FHR+ST, after training	
	Average	Range	Average	Range	Average	Range
US Raters (13)	47	37-64	53	41-67	69	43-88
EU Experts (7)	NA	NA	59	51-63	85	75-90

Table 4. % Agreement with True Intervention Status, as Defined by Cord Artery pH level (< 7.15 threshold), N=51 cases.

Secondary Hypotheses Effectiveness Evaluation

When the timing of the US investigators' decision to intervene was compared to that of the Swedish experts, the hypothesis was that the mean absolute difference between the Swedish experts and the US raters in the median time of intervention is less than 20 minutes. Neoventa Medical analyzed the proportion of cases in which the median times of intervention for the two groups differed by less than 20 minutes. The proportion of cases was 89% (8/9) for cases with pH level <7.05 (the Swedish experts did not intervene on one of these cases), and 60% (6/10) for cases with pH 7.05-7.14, for a total of 74% (14/19) for cases with pH <7.15. The number of cases is too small to draw statistical inference.

The US raters showed a wider variation in their assessment of FHR+ST data, as compared to the Swedish experts.

2. Clinical Use Study (CUS)

Study Objective

The objective of the CUS was to demonstrate that US obstetrical staff can appropriately use the STAN system, correctly interpret FHR+ST data and apply the STAN clinical use guidelines on a par with STAN experts. Another objective of the study was to demonstrate that the STAN system data can be properly used according to clinical guidelines yielding similar results to the results seen in the Swedish Randomized Controlled Trial.

Study Hypotheses

Primary Hypotheses

This study has the following co-primary hypotheses:

- Non-intervention by US clinicians will result in a normal outcome 75% or more of the time.
- US clinicians and a majority of the Swedish experts will agree to intervene 75% or more of the time and will agree not to intervene 75% or more of the time.

Primary Effectiveness Endpoints

- Negative Predictive Value (NPV). This value represents the probability that non-intervention results in a normal outcome in the cohort of infants with non-reassuring FHR (NRFHR) tracings, where normal outcome is defined as cord artery pH>7.12. NPV was defined as:

$$\frac{\#\text{ cases w/NRFHR, STAN allows continued labor, pH>7.12}}{\#\text{ cases w/NRFHR, STAN allows continued labor}}$$

The second primary hypothesis involved two endpoints:

- Positive Percent Agreement (PPA). This is the proportion of cases warranting intervention according to the STAN experts for which the US clinician decided to intervene at about the same time. Timing of the decision to intervene must be within ±20 minutes of the majority of STAN experts in the second stage of labor, and within ±30 minutes within the first stage of labor; and
- Negative Percent Agreement (NPA). This is the proportion of cases not warranting intervention according to the STAN experts for which the US clinician decided not to intervene.

The protocol pre-specified that since the US clinicians have clinical information available to them that is not available to the STAN experts, who only have the tracing, some failures to meet the above definition of agreement may be "overruled." Disagreements will each be reviewed, and if the disagreement is due to lack of relevant information by the STAN experts, those cases may be considered agreement.

Study Methodology

The US Clinical Use Study (CUS) was a prospective, non-randomized, uncontrolled multi-center trial. Thirty-nine clinicians participated at 6 sites, 3 of which were community hospitals and 3 of which were teaching hospitals. The study occurred in 3 phases: Education, Pilot, and Pivotal. Clinicians were trained during the Education Phase as described in the Education study above. They were required to pass the certification test before they could proceed to the Pilot Phase. In the Pilot Phase, they were required to complete 5 cases where fetal ECG data was collected but not used. These cases were then reviewed and discussed with either a Neoventa representative or a local expert appointed by Neoventa. This process was referred to as credentialing. Local experts were experienced physicians that have been through the credentialing process. Clinicians could not proceed to the Piv-

otal Phase until they had met certain goals including the demonstration of adequate understanding of STAN technology, concept, and methodology as determined by the Neoventa representative or Local expert. Sites could not proceed to the Pivotal Phase until at least 1 Clinician at the site had passed the credentialing process.

Inadequate Recordings and Signal Quality Problems during the CUS

In analyzing the data from the Swedish RCT, approximately 600 recordings were excluded because they were inadequate. Ninety-four percent of these inadequate recordings were attributed to failure to meet the 20 minute rule for setting the ECG baseline and/or lack of STAN data within 20 minutes of delivery.

During the Pilot Phase (Phase 2) of the CUS, 207 recordings were obtained, each of which consisted of at least 30 minutes of recording. Of these recordings 5.9% had signal quality issues.

During the Pivotal Phase (Phase 3) of the CUS, 95.4% of the spontaneous vaginal delivery cases had ST data within 20 minutes of delivery. Thirty four percent of the investigators reported that it was necessary to adjust the STAN monitor or sensor in order to improve signal quality. However, 88.3% of the investigators responded on a case report form that they "agreed" or "strongly agreed" that the STAN recording provided adequate information throughout labor. Therefore, the problem of inadequate recordings observed during the Swedish RCT had to a large degree been resolved. With respect to signal quality per se, 3 cases of signal quality problems were traced to a connector failure within the legplate cable that connects the scalp electrode to STAN. The manufacturer of the cable provided modified cables which helped resolve this issue.

In summary, the problem of inadequate recordings has been greatly reduced since the Swedish RCT. Signal quality issues persist but are largely addressed by adjusting the monitor or the sensor. An equipment malfunction accounted for a few cases of poor signal quality and that has been addressed, although one complaint that appeared related to the legplate was reported after the cables were modified.

Primary Hypothesis Effectiveness Evaluation

A total of 530 subjects was monitored.

Primary endpoint - NPV
For the protocol threshold of pH > 7.12 for a normal outcome, NPV was 95.2% (180/189) with 95% CI (91.2, 97.8%), based on 189 cases with NRFHR tracing. Because this pH threshold is somewhat arbitrary (and was different from the pH threshold for normal pH of $\geq$7.15 in the US Education Study), FDA requested that Neoventa Medical stratify the results for this endpoint over a range of pH values from 7.10 to 7.15. For each of these cut off points, the NPV was $\geq$ 92.6% and the lowest bound on the 95% CI was

87.9%. The target for success for this primary endpoint was met. This endpoint relates only to patients who experienced a period of non-reassuring fetal heart rate.

The per protocol definition of NPV given above included all cases for which STAN allowed continued labor, even if an intervention took place. In contrast, the traditional definition of NPV in this context would exclude all interventions. Therefore, NPV was recalculated under the following definition:

$$\frac{\#\text{ cases w/NRFHR, STAN allows continued labor, no intervention taken, pH>7.12}}{\#\text{ cases w/NRFHR, STAN allows continued labor, no intervention taken}}$$

Using this definition, the NPV was 95.5% (127/133) with 95% CI (90.4%, 98.3%). From the lower bound on the 95% CI, the primary hypothesis of NPV>75% was still met.

Primary endpoint - agreement on intervention
Two cases were excluded from PPA/NPA analysis. In one case, the STAN experts could not agree. In another case, the US clinician expressed both "failure to progress" and FHR+ST as cause for intervention and at the same time. Thus, 528 of the 530 cases were analyzed.

N=528	STAN Expert Majority Decision			
US Clinician Decision	No intervention	Intervention 2° to FHR concern outside STAN guidelines	Intervention 2° to FHR concern within STAN guidelines	Intervention 2° to FHR+ST concern within STAN guidelines
No intervention or intervention for failure to progress	444			5
Intervention 2° to FHR concern outside of STAN guidelines	31			
Intervention 2° to FHR concern within STAN guidelines	6			
Intervention 2° to FHR+ST concern within STAN guidelines	10		1	31

*or intervention for failure to progress

Table 5. Data Table for Calculation of NPA and PPA

NPA = 444/(444 + 31 + 6 + 10) = 444/491 = 90.4%

PPA = 31/37 = 83.8%

The STAN experts saw a need to intervene in 37 tracings. The US investigators saw a need to intervene in 79 tracings. These figures are not directly comparable because, as stated earlier, the US clinicians were responding to clinical events in labor and delivery to which the STAN experts were not privy. These included 47 cases in which the STAN experts would not have intervened. Thirty-one of these cases were ones in which events known to the US clinician and **not** within the purview of the STAN guidelines were the basis for the intervention. Therefore, there were 16 cases in which US clinicians correctly intervened according to STAN guidelines and STAN experts did not, and five cases in which STAN experts correctly intervened according to the guidelines and US investigators did not. All five cases had normal Apgar scores, cord acid base values and no need for special neonatal care. The clinical action of the US investigators was appropriate, although it did not meet the strict definition for agreement.

The PPA was 83.8% (31/37) with 95% CI (68.0%, 95.7%). The 95% CI lower bound indicates that the target value of > 75% was not met. Neoventa pointed out that the study was sized for showing PPA > 75% on the assumption that the true PPA is 90%. The 90% PPA was based on the rate of agreement to intervene in the Education Study. This rate did not take into account timing of intervention. When the Education Study data are re-calculated for **both** decision **and** timing of intervention, the new rate is 74% (14/19).

In the calculation of PPA, some technical disagreements were considered to be agreements because, as discussed above, US clinicians had clinical information not available to the STAN experts. Specifically, 17 spontaneous vaginal deliveries (SVD) were considered to be in positive agreement with the STAN expert decision to intervene on these same cases because the SVD occurred within 20 minutes of the time of the decision to intervene. Agreement on such cases was pre-specified in the protocol, but not whether it would be considered a positive agreement (for inclusion in PPA) or a negative agreement (for inclusion in NPA).

When these cases are excluded, PPA was 70.0% (14/20) with 95% CI (45.7%, 88.1%). The 95% CI lower bounds indicates that the hypothesis PPA>75% target value for PPA was still not met.

There were multiple analysis performed on these data, using different definitions for PPA, that also concluded that the 75% target was not met. The most important analysis of PPA was the original analysis in which the observed value for PPA was 83.8%. In considering that the lower bound on the 95% confidence interval of 68.0% was below the target value of 75%, it must be kept in mind that the study was not powered to detect a statistically significant PPA for this target value.

The NPA was 90.4% (444/491) with 95% CI (87.8%, 93.0%). The 95% CI lower bound indicates that the target value of > 75% was met. In the calculation of NPA, some technical disagreements were considered to be agreements because US clinicians had clinical information not available to

the STAN experts. Specifically, 82 interventions for failure to progress (FTP) were considered to be in negative agreement with the STAN expert decision to not intervene on these same cases. The first row of the exam matrix above is labeled to include this situation.

When these 82 cases are excluded, the NPA was 88.5% (362/409) with 95% CI (85.0%, 91.4%). The 95% CI lower bound indicates that the hypothesis NPA>75% target value for NPA was still met.

V. STAN TRAINING PROGRAM

A. Introduction

Adequate training is essential for the proper use and successful introduction of the STAN system. In addition to a standard in-service program, Neoventa has developed a comprehensive set of tools and programs for STAN clinical training. Neoventa will work with each institution to implement the following training program and make it self-sustaining.

The STAN Education program consists of 3 components

- Education and Certification
- Credentialing
- Continuing Education

B. Education and Certification Program

The objective of this phase is to educate the obstetric staff in STAN methodology and basic fetal physiology using the STAN education program. All physician and midwife care givers responsible for managing patients using STAN will be required to pass a certification test. Nursing staff will participate in similar training but certification will be optional.

The education program is an integral part of the STAN product and training material is included with the STAN device. The education program consists of:

- Textbook and interactive CD
- On-site training
- Certification process

Textbook and Interactive CD-ROM

Neoventa has developed a textbook and interactive CD entitled "Fetal Surveillance". The material covers basic physiology related to fetal hypoxia and fetal surveillance during labor and includes:

- Basic fetal physiology
- FHR physiology
- FHR interpretation
- Fetal ECG physiology (including identification of normal and abnormal ECG waveforms)
- Fetal ECG interpretation

- Assessment of the child

The CD-ROM contains interactive FHR/ST interpretation exercises and short quizzes. The materials are designed for self study prior to on-site training. Presentation slides are included that allow instructors to tailor training sessions.

Classification of FHR and Simplified Guidelines

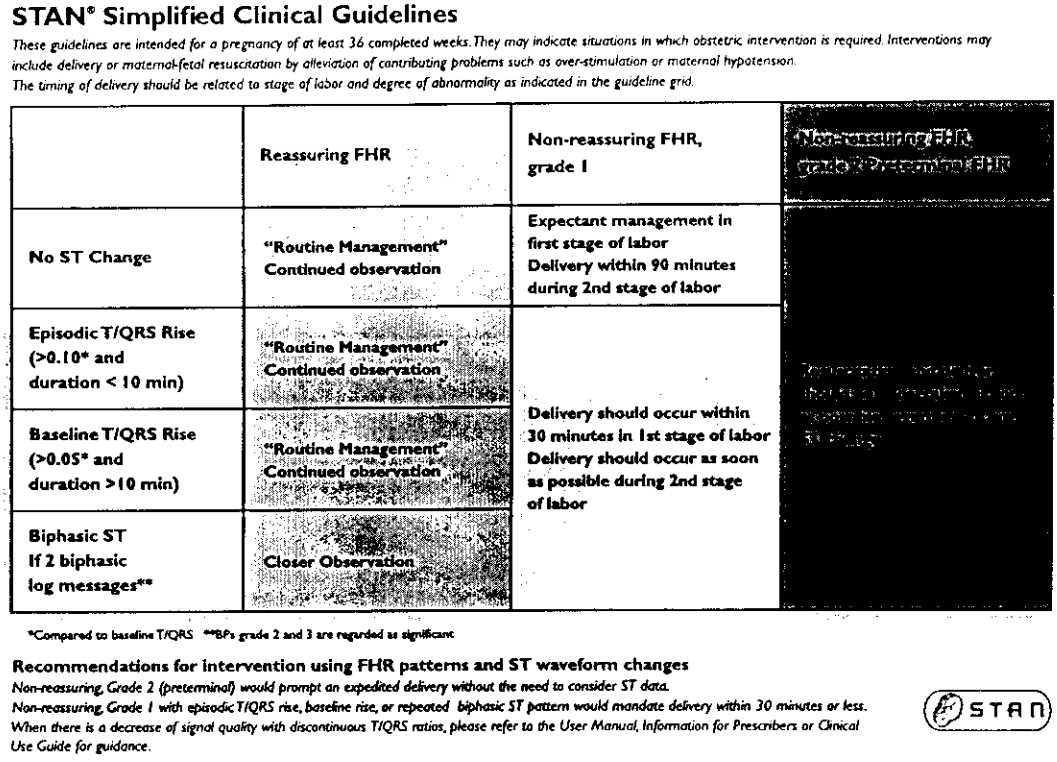
The following tables present the definitions of normal and abnormal FHR patterns as they apply to the STAN monitor and a matrix for making clinical management decisions using FHR + fetal ECG analysis. **These tables are recommendations only and are not intended to substitute for clinical decision making.**

Classification of FHR Patterns

FHR Classification	Baseline Heart Rate	Variability Reactivity	Decelerations
Reassuring	• 110-150 bpm	• 6-25 bpm • Accelerations present	• Early decelerations • Variable decelerations with a duration of < 60 sec and depth < 60 beats
Non-Reassuring, Grade 1	Bradycardia: • Rate < 110 bpm (without accelerations) • Episode > 2 minutes duration regardless of reactivity or variability Tachycardia: • Rate 150-170 bpm and minimal variability • Rate > 170 bpm	• ≤ 5 bpm for > 40 min • ≥ 25 bpm for > 40 min • Accelerations absent	• Variable decelerations with a duration of > 60 sec or depth > 60 beats • Repetitive late decelerations
Non-Reassuring, Grade 2 Pattern(s)	[illegible]	[illegible]	[illegible]

The intended use of this FHR classification system is to suggest clinical conditions in which adjunctive use of ST waveform changes may aid the interpretation of specific non-reassuring FHR patterns.

Figure 2. Classification of FHR Patterns



STAN® Simplified Clinical Guidelines

These guidelines are intended for a pregnancy of at least 36 completed weeks. They may indicate situations in which obstetric intervention is required. Interventions may include delivery or maternal-fetal resuscitation by alleviation of contributing problems such as over-stimulation or maternal hypotension.
The timing of delivery should be related to stage of labor and degree of abnormality as indicated in the guideline grid.

	Reassuring FHR	Non-reassuring FHR, grade 1	Non-reassuring FHR grade 2 Pretermina FHR
No ST Change	"Routine Management" Continued observation	Expectant management in first stage of labor Delivery within 90 minutes during 2nd stage of labor	
Episodic T/QRS Rise (>0.10* and duration < 10 min)	"Routine Management" Continued observation		
Baseline T/QRS Rise (>0.05* and duration >10 min)	"Routine Management" Continued observation	Delivery should occur within 30 minutes in 1st stage of labor Delivery should occur as soon as possible during 2nd stage of labor	
Biphasic ST If 2 biphasic log messages**	Closer Observation		

*Compared to baseline T/QRS **BPs grade 2 and 3 are regarded as significant

Recommendations for intervention using FHR patterns and ST waveform changes

Non-reassuring, Grade 2 (preterminal) would prompt an expedited delivery without the need to consider ST data.
Non-reassuring, Grade 1 with episodic T/QRS rise, baseline rise, or repeated biphasic ST pattern would mandate delivery within 30 minutes or less.
When there is a decrease of signal quality with discontinuous T/QRS ratios, please refer to the User Manual, Information for Prescribers or Clinical Use Guide for guidance.

STAN

Figure 3. STAN Simplified Clinical Guidelines

On-site training

On-site training consists of lectures and case discussions. Basic lecture material for the on-site training is available online at www.neoventa.com/US.

User certification

The certification test contains multiple choice questions which cover interpretation of STAN recordings and basic principles of intrapartum hypoxia and monitoring. Certification is mandatory for device use.

C. Credentialing Program

The objective of this phase is to allow the clinicians to gain experience with the STAN concept and technology by using the STAN system as a standard Electronic Fetal Monitor. ST information will be available, but not used to manage cases. All obstetric staff responsible for patient management during labor will monitor a minimum of 5 cases using the standard EFM data presented by STAN. The ST data will be observed, but not used for clinical management decisions. To ensure that quality recordings are obtained, there must be at least 30 minutes of tracings, a part of which is recorded within 20 minutes of delivery in all of the cases with spontaneous vaginal delivery monitored by the STAN system.

An experienced STAN user appointed by Neoventa will review the cases with the clinician to ensure that the STAN principles are understood. If the recordings are acceptable and the clinician understands the methodology, they are credentialed and may use STAN clinically.

Case Management

Labor will be managed according to standard EFM clinical practice. ST information will not be used to manage cases during this phase.

Credentialing Criteria

The credentialing process includes:

- Successful completion of the Certification Test
- Acceptable STAN tracings at least 30 minutes in length with a part of the recording occurring within 20minutes of delivery in case of a spontaneous vaginal delivery.
- Review and discussion of case tracings and clinical data to ensure understanding of the STAN concept and methodology

D. Continuing Education

To facilitate continuing education, Neoventa has developed an Internet site (www.stancases.com), which contains regularly updated sample cases. Key cases include clinical discussion.

Neoventa recommends that STAN users review these cases regularly to increase their exposure to different patient management situations.

E. Recredentialing

Credentialing tests are updated by Neoventa every 6-12 months.

Neoventa recommends STAN users to recredential themselves on a yearly basis. The latest credentialing tests will be available online at www.neoventa.com.

GENERAL

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Other Manuals

STAN S31 Fetal Heart Monitor User Manual - PRD 101 003

STAN S31 Fetal Heart Monitor Service Manual - PRD 101 004

STAN S31 Fetal Heart Monitor Clinical Use Guide - PRD 101 014