Computer Alerting Monitoring System 2 (CALMS-2 study)

Improving management of post-operative upper GI surgical patients.

Protocol Version 2.2

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Chief Investigator:	Dr Peter Watkinson
Investigators:	Professor Lionel Tarassenko Dr Duncan Young Mr Nick Maynard Dr Jonathan Salmon
Sponsor:	Oxford Radcliffe NHS Trust
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Signatures:	

Confidentiality Statement This document contains confidential information that must not be disclosed to anyone other than the Sponsor, the Investigator Team, host NHS Trust(s), regulatory authorities, and members of the Research Ethics Committee.

Amendment History

Amendment No.	Protocol Version No.	Date issued	Author(s) of changes	Details of Changes made
1	2.0	February 2011	Sarah Vollam/Peter Watkinson	Updated in line with new IRAS application to add non-CE marked software to investigational device. NOT REC APPROVED
2	2.1	April 2011	Sarah Vollam/Peter Watkinson	Addition of consultee for patients who lose capacity
3	2.2	June 2011	Sarah Vollam/Peter Watkinson/Teresa Saunders	Removal of continuous respiratory estimation software.

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Synopsis

Study Title	**Computer Alerting Monitoring System 2 (CALMS 2)**
Internal ref. no.	
Type of study	Clinical trial of electronic versus paper based observation charting
Trial Design	Controlled Trial
Trial Participants	High-risk upper gastro-intestinal surgical patients
Planned Sample Size	400
Planned Trial Period	26 months in four phases (phases 1 and 2 – (13 months) already completed)
Primary Objective	Does continuous monitoring of 'vital signs' with computer-modelled alerting to detect patient deteriorations reduce patients' length of stay in hospital by alerting staff to clinical deteriorations more effectively than current paper-based systems?
Secondary Objectives	Does continuous monitoring of 'vital signs' with computer-modelled alerting to detect patient deteriorations reduce mortality in this group of high-risk surgical patients? Does continuous monitoring of 'vital signs' with computer-modelled alerting to detect patient deteriorations reduce the number of unplanned admissions to Intensive Care from the ward? Is there a difference in the period between computer-modelled alerting and defined clinical deteriorations, compared with the period between 'Track-and-Trigger' alerting and defined clinical deteriorations? To demonstrate the sensitivity, specificity, positive and negative prediction values of computer-modelled alerting compared with 'Track-and-Trigger' alerting for defined clinical deteriorations.
Primary Endpoint	Length of stay (admission to ward post-surgery to discharge from ward) in patients pre- and post-intervention.
Secondary Endpoints	Patient outcome measures: • the numbers of clinical events recorded in patients pre- and post- intervention Compliance measures (paper-based 'Track-and-Trigger' system versus 'Computer-Modelled Alerting System'): • the sensitivity of the monitoring system used • the specificity of the monitoring system used • the positive predictive value of the monitoring system used

	• the negative predictive value of the monitoring system used
Device Name	Visensia Version 3.1
Manufacturer Name	OBS Medical
Principle intended use	Vital signs monitoring with smart alerting system for identifying physiological deterioration
Length of time the device has been in use.	

Background and rationale

Over the last five years, the Department of Engineering Science, in collaboration with clinicians at the John Radcliffe Hospital (ICU and Kadoorie Centre), has been developing a multi-parameter monitoring system based on the *data fusion* of vital sign parameters.

Unlike conventional 'Track-and-Trigger' systems (paper-based vital signs charts which assign a score to each measured parameter according to how 'abnormal' it is), this has involved *learning* a model of "normality" from data acquired from high-risk adult patients in hospital. An alert is generated whenever the vital sign parameters are abnormal enough to be outside the "95% envelope of normality" captured within the learnt data fusion model. The current system generates a score known as the Visensia Index VSI. In a recent study in the US, the use of VSI in place of a standard 'Track-and-Trigger' score has led to more rapid identification of sick patients, faster treatment and a significant reduction in serious events.

Unlike standard 'Track-and-Trigger' scores, the VSI is continuous, which allows more precise calibration for individual patient groups and, potentially, easier identification of adverse trends. "Tuning" for particular patient groups might be expected to increase the positive predictive value of the system.

Patients who undergo major upper gastro-intestinal (GI) surgery have a high (up to 50%) incidence of post-operative complications. These complications are frequently delayed; despite an apparently straightforward peri-operative course and initial

recovery, patients may require admission to the intensive care unit (ICU) several days after surgery, most commonly with respiratory failure or anastomotic leaks. Their subsequent stay in ICU is prolonged and their mortality is high. They utilise more ICU resources than any other group of surgical patients. A calibrated alerting system with a high positive predictive value should lead to earlier identification of complications and hence improvements in outcomes for patients undergoing upper GI surgery.

CALMS 2 aims to demonstrate the predictive value of this system in patients undergoing upper GI surgery. The first and second phases of this study have already been completed, and have resulted in the development of a 'model of normality' for this group of patients. In phases three and four, this 'model of normality' will be incorporated into the study system. In order to make improvements in the usability of this system based on feedback from phase two, non-CE marked software has been added to the previously CE-marked system, which has required resubmission for ethical approval.

Objectives

Programme aims:

The overall aims of the programme are to:

- Provide enhanced decision support on the upper GI surgical ward and ICU (where other information such as blood chemistry is also required for the models) and maximise the benefit of early intervention in Upper GI surgery.

- Establish the Oxford Cancer Centre (especially the Upper GI Surgical Department) and Churchill ICU as centres of excellence for the development and application of track-and-trigger technology for the management of acutely ill patients.

Primary objective:

To assess whether continuous monitoring of 'vital signs' with computer-modelled alerting to detect patient deteriorations reduces patients' length of stay in hospital by alerting staff to clinical deteriorations more effectively than current paper-based systems.

Secondary objectives:

To assess whether continuous monitoring of 'vital signs' with computer-modelled alerting to detect patient deteriorations reduces mortality in this group of high-risk surgical patients.

To assess whether continuous monitoring of 'vital signs' with computer-modelled alerting to detect patient deteriorations reduces the number of unplanned admissions to Intensive Care from the ward.

To assess whether there is a difference in the period between computer-modelled alerting and defined clinical deteriorations, compared with the period between 'Track-and-Trigger' alerting and defined clinical deteriorations.

To demonstrate the sensitivity, specificity, positive and negative prediction values of computer-modelled alerting compared with 'Track-and-Trigger' alerting for defined clinical deteriorations.

Specific Year 1 objectives – already achieved in phase and 2:

To recruit 200 patients to this study from the Upper GI Ward.

To tune (calibrate) the Computer-Modelled Alerting System's 'model of normality' to upper GI surgical patients.

Specific Year 2 objectives:

To recruit 200 patients to this study from the Upper GI Ward.

To utilise the tuned 'Computer-Modelled Alerting System' for upper GI surgical patients to alert staff to clinical deterioration.

Study design

A pre- and post- intervention design is being used, as a randomised controlled trial is not possible because of the unblinded intervention being assessed. Were patients on the same ward to be monitored with the two different systems ('Computer-Alerting Monitoring System' and 'Track-and-Trigger' system) the 'Computer-Modelled Alerting System' would cause a "learning effect" (recognition between deteriorating vital signs and the VSI score) and treatment of the control group would alter. Cases will be matched with those from a comparator unit to allow identification of national trends in length of stay over time in these patients which might confound the results.

The study hypothesis is that an automated, population-calibrated, multi-modal alerting system will better identify patients after upper GI surgery who are at risk of clinical deterioration than a standard paper based 'Track-and-Trigger' system (a system that give a score for heart rate, respiratory rate, blood pressure and blood oxygen levels).

All elective upper GI surgical patients are managed on a single ward. 3-5 patients are admitted each week for major surgery and up to 12 patients may be suitable for monitoring at any one time (this number fluctuates over a seven day period). The study will be divided into four phases, the first two of which have been completed - as follows:

Phase One (1 month) - *COMPLETED*

This consisted of training the research nurses in the processes of the trial and on the technology utilised.

Phase Two (1 year, 200 patients) - *COMPLETED*

Phase two had two purposes, to generate the control group ("pre-intervention") data and to calibrate the data fusion algorithm. The study design allowed both to proceed simultaneously.

Consenting patients were monitored using conventional 'Track-and-Trigger' scoring until deemed fit for discharge by the surgical team. A 'Track-and-Trigger' alarm activated a clinical response algorithm, which included rapid review by Intensive Care services.

Simultaneously, all consenting patients were monitored from first return to the ward with the normal ward bedside monitor with study system attached. Patients were then transferred to a telemetry monitoring system which allowed continuous monitoring of heart rate and pulse oximetry combined with intermittent blood pressure, respiratory rate and temperature recordings until the patient was deemed fit for discharge by the surgical team. The results of the 'Computer-Modelled Alerting System' (i.e. the derived vital signs score) were not be available to the attending staff.

A standard dataset including available biochemistry results was also collected by the research team.. This data has been used to "tune" the current 'Computer-Modelled Alerting System' for this patient group, providing a 'model of normality' on which to base the alerts.

Phases one and two have already been completed.

Phase Three (1 month)

The 'Computer-Modelled Alerting System' will be employed at each monitored bed space. Staff will be educated in its use but will not be asked specifically to use it in clinical decision-making.

Phase Four (1 year, 200 patients)

The 'Computer-Modelled Alerting System' will be in place, utilising the monitoring data from each patient. All consenting patients will be monitored from first return to the ward. Initially this will be using a bedside monitor with the study system attached. When fit enough to get out of bed, patients will be transferred to a telemetry system (which is designed to be portable) which will allow continuous monitoring of heart rate

and pulse oximetry combined with intermittent blood pressure, respiratory rate and temperature recordings until the patient is deemed fit for discharge by the surgical team (as in phase two). The main difference between these two monitors is the freedom of the patient to move around while attached. Further details of this system can be found below. The 'Computer-Modelled Alerting System' will be used overtly in clinical decision-making, with staff using a clinical algorithm response, which will include rapid review by Intensive Care services. Throughout phase four the standard 'Track-and-Trigger' system will remain in use, as per normal care on the ward. Data will be collected as in phase two.

Criteria for discontinuing monitoring:

- When the surgical team has deemed the patient fit for discharge
- Patient request to have monitoring removed
- Death
- Transfer to a hospital outside of the ORH Trust
- Transfer to the Intensive Care Unit

Study duration: The study is estimated to last for 26 months. Patients who agree to enter the study will only have data collected for the duration of their acute hospital stay. There will be no further follow up for the purposes of this study.

Primary endpoint: Length of stay (admission to ward post-surgery to discharge from ward) in patients pre- and post-intervention.

Secondary endpoints:

Patient outcome measures:

- the numbers of clinical events recorded in patients pre- and post- intervention

Compliance measures (paper-based 'Track-and-Trigger' system versus 'Computer-Modelled Alerting System'):

- the sensitivity of the monitoring system used
- the specificity of the monitoring system used
- the positive predictive value of the monitoring system used

Study population: 400 patients – 200 in phase two *(already completed)* and 200 in phase four.

Study participants:

The study participants will have upper gastro-intestinal cancer for which surgery has been performed. Patients who undergo this type of surgery are at high risk for complications such as respiratory failure, anastomotic leaks, infections and bleeding.

Inclusion criteria: All patients admitted to the Oxford Radcliffe Hospitals NHS Trust for Upper Gastro-Intestinal Surgery, who are willing and able to give consent. This will include patients undergoing the following procedures: oesophagectomy, oesophagogastrectomy, gastrectomy, whipples, liver resection, pancreatectomy, gastric bypass, billiary reconstruction and splenectomy.

Exclusion criteria:

- patients refusing consent,
- children (less than 16 years old),
- prisoners,
- pregnant women,
- patients whose anatomy precludes the use of the required monitoring,
- patients who are judged to lack capacity at the time of consent,
- patients who cannot understand written English and for whom no translator can be found.

Withdrawal: Subjects may withdraw at any time; the reason for their withdrawal will be recorded in the study data collection. Patients who wish to withdraw from further involvement in the study will be asked whether it is possible to use the data collected up to the point of withdrawal.

Informed consent: The National Information Governance Board has been successfully approached for support under section 251 of the NHS act 2006 to process patient identifiable information without consent. This is required to allow for eligibility

screening prior to approach, and accessing of information required for postal contact of eligible patients (name and postal address). Screening for eligibility will involve the research nurses accessing Pre-Operative Assessment (POA) clinic lists through the local trust Patient Administration System (PAS), from which patients undergoing eligible procedures will be identified. Research nurses will also be sent theatre lists via e-mail from the surgical secretaries, to ensure that any patients who do not visit the pre-operative assessment clinic are not missed.

The name and POA clinic dates for those patients awaiting approach will be held on a secure database on the NHS computer of Dr Peter Watkinson (Principal Investigator). This computer will be password protected, and kept in a research facility behind two locked doors which require key card access. This data will be held until the point of approach only. At this time those patients who refuse participation in the study will be asked to sign a consent form to allow retention of minimal information (name and hospital number) on this database, in order to ensure they are not approached again. If they decline this consent, all of their patient identifiable information will be destroyed. All further identifiable patient information accessed and retained will be with explicit consent of the study subjects.

The consent process will be as follows:

1. Those patients scheduled to have a suitable operation will be sent a covering letter and patient information sheet before their POA clinic appointment. These individuals will then be approached in POA clinic by a member of the research team (primarily the research nurse) to ask if they have received the information

sheet, if they have any questions regarding the study, and then for their consent or refusal to enter the study.

2. A small minority of patients may not attend the POA clinic, however these patients will still be sent a study covering letter and information sheet, and approach for their consent or refusal will occur on admission to the ward prior to their surgery by a member the research team (primarily the research nurses).

Loss of capacity to consent: We expect that some patients who deteriorate are likely to lose capacity to consent, at least temporarily, because of this deterioration. Since the monitoring equipment is likely to prove especially beneficial to these patients, and a full evaluation of its value cannot be made without studying them, we feel it is justified to seek to continue using the equipment during this phase of their illness.

Under the Mental Capacity Act (2005) a person **lacking capacity** is defined as someone unable:

- To understand information relevant to the decision
- To retain that information
- To use or weigh that information
- To communicate a decision

The research nurses will decide on the capacity of the patients to provide/affirm consent at each interaction with the patient. The assessment regarding their capacity will be made in line with the Mental Capacity Act. The quality of consent will be ascertained from the responses given during each interaction. Questions will

be encouraged and an opportunity to clarify information provided. All research nurses will be trained in the consent process by our current experienced research nursing staff. They will also complete an on-line good clinical practice course which contains capacity training (provided by the University of Oxford) and the Oxford Radcliffe NHS Trust's on-line Mental Capacity Act (2005) on-line course. The named nurse for the patient will also be consulted, as being best placed to inform the research nurse of any reservations voiced or exhibited by the patient.

For those deemed to lack capacity to confirm their consent to continue in the study, The Department of Health 'Guidance on Nominating a Consultee for Research Involving Adults Who Lack Capacity To Consent' document will be used to guide the identification of a consultee, which preferably will be a 'personal' consultee (a family member or friend). Where this is not possible we will seek a 'nominated' consultee.

A personal consultee will be contacted with the assistance of the ward nurse caring for the patient at the time of deterioration, and will be, wherever possible, the next of kin or a close family member/friend. In most cases where a patient deteriorates, their family will be present or contacted by the ward staff. Where this is not the case, the next of kin will be contacted by telephone by the research nurse and met in person at the earliest opportunity.

Where a personal consultee is not available, a nominated consultee will be sought. Instances where this may be required include:

- where no family member or friend is willing and able to act as consultee
- where the family or friends live a long distance away and/or are not in frequent contact with the person who lacks capacity
- where the regular carers of the person who lacks capacity are doing so for payment or in a professional capacity (e.g. care home staff or nurses)
- where someone is acting in a professional role (e.g. their GP or solicitor).

The hospital trust does not currently have a panel of suitable consultees which we could access. Following the DH guidance, it is believed that a senior member of the surgical team would be best placed to act as a nominated consultee in the absence of anyone available or willing to act as personal consultee. The surgical team are not in any way connected with the study, and are well placed to have established a relationship with the patient over several weeks of treatment. The nominated consultee will, wherever possible, consult with any available person who has knowledge of the patient, e.g. via telephone with a relative who is unable to visit the patient.

The DH document outlines the role of the consultee in respect to a participant's loss of capacity in the course of a study he/she has already consented to. They advise that the consultee should understand that the participant has already consented to the study, but should be encouraged to consider any factors which they believe may be relevant to this initial consent, in light of their deterioration. The document also advises that it should be made clear that they are not consenting to any further data collection or interventions than those initially consented to.

Study assessments:

Study nurses will extract the following information from the patient's notes and enter it into a trial specific data entry form:

1. The date and type of operation, and surgeon
2. The date and time of admission to the ward
3. In-hospital mortality
4. Admissions to Intensive Care – planned or unplanned.
5. Daily clinical events – defined by a pick list (including cardiac arrest calls, specified emergency treatment, antibiotics, etc.)
6. Returns to theatre, including procedure – defined by a pick list
7. Relevant daily biochemistry results (urea and potassium)
8. All charted vital signs observation sets, including 'Track-and-Trigger' scores
9. The date and time of discharge as recorded on the hospital admissions system.
10. The "fit-to-discharge" point.

Interventions

All patients who agree to take part in the study will be attached initially to a standard hospital monitor and later a portable monitoring system, both of which are linked to the 'Computer-Modelled Alerting System'.

The ‘Computer-Modelled Alerting System’ comprises two types of monitor – a bedside monitor for the initial admission period (usual care on the ward is connection to this bedside monitor in the immediate post-operative period), and a portable monitor for ambulatory patients. The bedside monitoring equipment consists of a panel PC mounted on the bedside monitor used in normal ward care, a central display screen, software and a data store. The ambulatory system consists of a pulse oximeter with a soft finger probe, a PDA which connects the pulse oximeter with the central screen, software, including the additional non-CE marked software, and a data store. Generally, the patient will be attached to the bedside monitor in the immediate post-operative period and transferred to the ambulatory monitor when they are fit enough to get out of bed. In some instances, the patient’s condition may deteriorate during their recovery and they will consequently be placed back on the bedside monitor as part of the normal care of the ward. This will be at the ward nurses’ discretion and will not affect the study, as data is collected from both systems.

The ‘Computer-Modelled Alerting System’ is capable of recording and processing physiological variables from various sources. For the bedside monitoring system these comprise of:

- *Single channel 3 lead ECG*. The leads will be arranged in a standard CM5 configuration, or in a configuration which elicits the best impedance pneumogram trace.

- *Impedance pneumograph*. This is derived from the impedance at 63 kHz between the left and right ECG electrodes and does not require separate leads.

- *Pulse oximeter*. The probe will be a reusable soft finger probe. Recorded continuously.

- *Non-invasive blood pressure*. This is a standard oscillometric non-invasive blood pressure system.

- *Tympanic temperature.* This can be entered manually by the nursing staff, via the panel PC attached to the bedside monitor.

Pulse rate and oxygen saturations are recorded continuously. Non-invasive blood pressure, respiratory rate and temperature are recorded intermittently. Blood pressure is automated to record every 30 minutes initially, however, after attachment the nurses and clinicians on the ward are free to configure the monitor and its alarms as they deem appropriate for the clinical situation.

The vital signs data from the monitor pass to a data recording panel PC module mounted with the monitor, via the serial port (RS432) from the monitor. This module records the data in real time, and stores both the raw signals and the derived variables onto the hard disk with a time signature. The monitoring system uses the patient isolation in the commercial monitor to ensure appropriate electrical isolation. The vital signs data are then transferred to the central screen via the secured hospital Wi-Fi network.

For the portable monitoring system the sources of physiological variables are as follows:

- *Pulse oximeter*. The probe will be a reusable soft finger probe. The pulse oximeter will measure both oxygen saturations and pulse rate. This information will be transmitted via blue tooth to the Personal Digital Assistant (PDA) assigned to each pulse oximeter

- *Respiratory rate*. Will be entered by the nursing staff onto the assigned PDA.

- *Non-invasive blood pressure*. Will be entered by the nursing staff onto the assigned PDA.

- *Tympanic temperature.* Entered onto PDA by the nursing staff, as above.

Pulse rate and oxygen saturations are recorded continuously. Respiratory rate, non-invasive blood pressure and temperature are recorded intermittently. The vital signs data are transferred from the PDA to the central screen via the secured hospital Wi-Fi network.

At the central screen, data from either the bedside or ambulatory monitor are displayed, the data fusion occurs and the derived scores and alerts are displayed. The central screen also displays patient name (to allow linkage of alerts with patient), connectivity messages (to highlight when monitoring has been removed) and alert status (if the alert has been silenced). The central monitor allows nursing staff to silence alerts for a brief period, acknowledge alerts to allow time to respond, and

change the threshold of alerts if required. The system is accessible to the research staff to allow input of patient identifiers, the offloading of data and maintenance. In phase 2 the system gives no indication of any computed variable to the clinical staff, though it does have an indicator to show it is functioning. In phase 4 it will be visible to the clinical staff.

In Phase 2 of the study the 'Computer-Modelled Alerting System' recorded data but was not visible to clinical staff. In Phase 4 the 'Computer-Modelled Alerting System' (utilising the 'model of normality' derived from phase 2) will be used overtly in clinical decision-making, with staff using a clinical response algorithm. In both phases of the study the ward nurses will be recording paper based "Track-and-Trigger" scores, and acting on these if they equal or exceed the set ward threshold. In phase 4 this will occur in addition to the computer-modelled alerts.

Maintenance and storage of devices:

The bedside monitors will be stored on the ward, and cleaned using standard antibacterial cleaning materials used in trust.

The ambulatory monitoring equipment will be stored in the secure research facility and cleaned using standard antibacterial cleaning materials used in the trust.

Maintenance of the devices will be done by the manufacturers.

Data capture

Non-ambulatory patients: physiological data from the (Philips) monitor will be downloaded using a direct connection onto a Toughbook running Visensia software which will display the physiological values (as does the Philips monitor) along with the calculated risk score.

Ambulatory patients: will be monitored using a Nonin Avant 4100 Pulse Oximeter. Information from the Nonin Avant 4100 is sent over a Bluetooth connection using at least Security Mode 3 to Visensia Enabling PDAs (HTC Touch 3G devices – no SIM). The PDA has three functions:

1. Software running on the PDA decodes information from the Nonin Avant 4100, which is then transmitted over the Oxford Radcliffe NHS secure Wi-Fi to the Visensia server.
2. Information from the Visensia server (physiological values and the calculated risk score), transmitted over the Oxford Radcliffe NHS secure Wi-Fi, is displayed on the PDA.
3. Nursing staff input standard physiological observations (blood pressure, temperature, and respiratory rate) onto the PDA. These values are both displayed and relayed to the Visensia server. PDA's are secured using a four digit PIN.

The values and score from both non-ambulatory and ambulatory monitoring will be sent via the secure Oxford Radcliffe NHS Wi-Fi to the Visensia server running on the secure Oxford Radcliffe NHS server farm, where all data is logged with patient identifiers (this server farm is used to store all NHS clinical data). . The physiological values and calculated risk score will be displayed along with patient's name and

hospital number via the secure Oxford Radcliffe NHS network on two Captec panel personal computers to allow remote monitoring within the ward. This vital signs display will also be available on a dumb terminal in the secure research facility, to allow connectivity monitoring by the research nurses.

Study nurses will collect clinical event data and paper-based track-and-trigger data using a research laptop. Access to the laptop will be restricted to research nurses, using username and 8 digit passwords (including alphanumeric and special characters). The laptop stores no data, but serves as a device to open and populate secure database files on the secure NHS network, without taking a local copy, via the secure NHS Wi-Fi. Database files will be stored on the secure Oxford Radcliffe NHS server farm. Patient data will be identified with the patient hospital number only.

Research nurses will need to have access to the patient's medical record to enable linkage with the research data, and to assess patient outcome measures. It would not be practical to train and monitor all of the nurses in the direct care team in collecting this data, and it would prove a burdensome addition to their workload. Access to this patient data is explicitly included in the consent process.

Analysis of data

For the purposes of analysis, each participant will be given an individual study number when they consent to take part in the study. The study number will be kept with the patient’s name, hospital number and demographic data on the master log. This will be held on the NHS computer of Dr Peter Watkinson, within the secure research facility (behind two doors, one security-lock protected, one swipe-card

protected). The master log will be backed up onto the secure NHS server farm, the security of which is described above. Access to the master log will be restricted (by username and 8 digit password, including alphanumeric and special characters) to Dr Peter Watkinson and the research nurses.

Automatic anonymisation of patient-confidential data will take place in a dedicated computer, on the NHS network, located behind two card-locked doors in the John Radcliffe Hospital, to which only the Principal Investigator and Research Nurses will have access. The anonymisation software will be operated by the Research Nurses, using a master log that records the mapping from patient-confidential data (such as 7-digit NHS hospital ID) into anonymised study identifiers (such as a 5-digit numeric code; e.g., "Patient 00321"). Access to the master log will be restricted to the Principal Investigator and Research Nurses, as described elsewhere. The resulting anonymised data will be written to an encrypted external hard-disk drive connected to the dedicated anonymisation computer. The Research Nurses will then disconnect the external drive from the anonymisation computer (on the secure NHS network) and connect it to a dedicated computer (situated in the same secure room as the anonymisation computer) on the secure Oxford University network for analysis. Access to this computer will be restricted by password to Professor Tarassenko and his Research Assistants. The anonymised data will be copied by encrypted FTP (using the restricted passwords) to the Institute of Biomedical Engineering, for further analysis by Professor Tarassenko and his Research Assistants. This latter anonymised copy will be stored on encrypted hard-disk drives (access restricted by password), which are situated behind two card-swipe doors and a locked door. Periodic archival back-ups of the anonymised data will be performed

automatically by the Oxford University secure data-archive system, which is used for archiving data from many clinical trials across the university.

Analysis of data will take place on University PCs, accessing data on a restricted area of a file server (running Novell Netware). Access will be restricted (via network log-in with a user name and passwords to be a minimum of 8 characters including both upper and lower case alphanumeric characters) to Dr Peter Watkinson, Professor Lionel Tarassenko, his research assistants and the research nurses. Intruder lockout by default operates on 5 incorrect login attempts in 30 minutes causes a 1 hour account lockout.

The end of the trial

The trial will end following recruitment of 400 patients. The trial will only be stopped prematurely if mandated by the ethics committee or competent authority.

Safety reporting

Reporting of AE: All AE's occurring during the study observed by the investigator or reported by the participant, whether or not attributed to the device under investigation will be recorded on the CRF as specified in the protocol.

A completed ORH SAE reporting form (http://www.oxfordradcliffe.nhs.uk/research/documents/Template-SeriousAdverseEventsReportingForm-ORHv1.doc) should be faxed to the Principal Investigator (fax: 01865 857611). The following information will be recorded: description, date of onset and end date, severity, assessment of relatedness to device,

other suspect drug or device and action taken. Follow-up information should be provided as necessary.

The Principal Investigator will report all serious adverse event (SAE)/serious adverse device event (SADE)/unanticipated adverse device effects (UADE)s (for definitions see appendix 4) will be reported to the Oxford Radcliffe Hospital Research and Development department as the sponsor and the manufacturer within one working day of the investigator team becoming aware of them using the ORH SAE reporting form (by fax: 01865 222648) giving as much information about the incident as possible, and will be signed by the PI or Co-investigator. The Research and Development Department will acknowledge receipt of the event documentation within two working days. The principal investigator will include an assessment as to whether the study can proceed; any changes necessary to the protocol should be included in this assessment. The ORH R&D Department will undertake an initial review of the information and ensure it is reviewed by the ORH/University of Oxford Trial Safety Group Medical Monitor. Events will be followed up until resolution, any appropriate further information will be sent by the research team in a timely manner. The relationship of AEs to the device will be assessed by a medically qualified investigator or the sponsor/manufacturer and will be followed up until resolution or the event is considered stable.

Reports of related and unexpected SAEs will be submitted to ethics within 15 days of the Chief Investigator becoming aware of the event, using the SAE report form for non-CTIMPs published on the National Research Ethics Service serious adverse event

form (appendix 2): http://www.nres.npsa.nhs.uk/applications/after-ethical-review/safetyreports/safety-reports-for-all-other-research/

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Reporting to the MHRA will be done in liaison with the Chief Investigator and the Manufacturer.

The manufacturer has a legal obligation to report all events that need to be reported to the Nominated Competent Authority immediately (without any unjustifiable delay) after a link is established between the event and the device, but no more than:

- 2 days following the awareness of the event for Serious Public Health Threat.
- 10 days following awareness of the event for Death or unanticipated serious deterioration in health.
- 30 days following the awareness of the event for all other event meeting the SAE criteria.

All ADE that result in a participant's withdrawal from the study or are present at the end of the study, should be followed up until a satisfactory resolution occurs.

Annual Reports: In addition to the above reporting the Chief Investigator will submit once a year, throughout the trial, or on request a progress/safety report to the REC and R&D.

Statistics

Randomisation and power calculation: If the Software Monitor data fusion system has a clinically significant effect by avoiding or decreasing the severity of clinical deteriorations by appropriate early warning, it should cause a clinically significant reduction in the length of stay. The study is powered to detect a 2-day reduction in length of stay, corrected for in-hospital mortality, (80% power, p=0.05), as the primary endpoint.

There is no randomisation involved in this study.

Number of participants: 400 complete data sets from patients are required for this study – 200 from phase two (already completed) and 200 from phase four (there is no recruitment in phases one and three).

Procedure for Accounting for Missing, Unused, and Spurious Data: All data will be double entered into an SQL database by two trial nurses. Missing/discordant data fields will be automatically flagged to allow resolution.

Procedures for Reporting any Deviation(s) from the Original Statistical Plan: The trial will be registered (EUDRACT). Any change in the statistical plan will be reported both to EUDRACT and in the final report.

Inclusion in Analysis: The outcomes of all patients allocated to each phase (2 and 4) will be analysed on an intention-to-treat basis (primary outcome). The outcomes of

those who actually received the intervention (electronic monitoring) will also be analysed.

Ethics

The National Information Governance Board has been successfully approached for support under section 251 of the NHS act 2006 to process patient identifiable information without consent, in order to allow pre-operative assessment lists to be screened for eligible patients, and those patients to be invited, by post, to participate in the study. No feasible alternative to this approach could be identified.

Declaration of Helsinki: the Investigator will ensure that this study is conducted in accordance with the principles of the Declaration of Helsinki.

ICH Guidelines for Good Clinical Practice: the Investigator will ensure that this study is conducted in full conformity with relevant regulations and with the ICH Guidelines for Good Clinical Practice (CPMP/ICH/135/95) July 1996.

Approvals: the protocol, informed consent form, participant information sheet and any proposed advertising material will be submitted to an appropriate Research Ethics Committee (REC), regulatory authorities and host institution(s) for written approval. The Investigator will submit and, where necessary, obtain approval from the above parties for all substantial amendments to the original approved documents.

Participant confidentiality: All members of the research team will have confidentiality clauses in their contracts and will be well informed of the NHS code of confidentiality and the Caldicott principles. The trial staff will ensure that the participants' anonymity is maintained. Patients will be assigned a trial number through a case report file (CRF). All patient data will be connected to this number when stored electronically. Patient names or other identifiers will be recorded in a separate, secure database accessed only by the research nurses and Principal Investigator. All trial paperwork will be held in a locked file behind two locked doors. The trial computer, on which analysis of the anonymised data will take place will be password-protected and kept in a research-specific area behind two locked doors. The electronic 'Computer-Modelled Alerting System' will be protected by the Oxford Radcliffe NHS Trust electronic security system (see network security policy v2). The study will comply with the Data Protection Act 1998 which requires data to be anonymised as soon as it is practical to do so.

Data monitoring

The study may be monitored or audited by representatives of the ORH Research and development department for compliance with the Department of Health Research Governance Framework for Health and Social Care 2005.

Direct access to data/source documents

Direct access will be granted to authorised representatives from the sponsor, host institution and the regulatory authorities to permit trial-related monitoring, audits and

inspections.

Trial funding

The trial will be funded by the Biomedical Research Council. At the time of print this totalled £542,677.

NHS bodies are legally liable for the negligent acts and omissions of their employees. If a patient is harmed whilst taking part in a clinical trial as a result of negligence on the part of a member of the study team this liability cover would apply.

Non-negligent harm is not covered by the NHS indemnity scheme. The Oxford Radcliffe NHS Trust, therefore, cannot agree in advance to pay compensation in these circumstances. In exceptional circumstances an ex-gratia payment may be offered.

Publication Policy

The lead author for all papers will be Dr Peter Watkinson**.** The authors have no vested interest in the results, which will be published regardless of outcome, in peer-reviewed journals. The final version will be agreed by the steering committee before submission.

Study Personnel

Principal Investigator: Dr Peter Watkinson

Co-investigators: Dr Jonathan Salmon, Dr Duncan Young, Mr Nick Maynard, Professor Lionel Tarassenko

Research Nurses: Sarah Vollam, Deborah Evans, Teresa Saunders

Statistician: Dr Jacqueline Birks

Appendix 1: Oxford Radcliffe SAE form

SAE No (for office use only): ☐☐☐

Oxford Radcliffe Hospitals NHS
NHS Trust

Serious Adverse Events Reporting Form

No of Pages including attachments ☐☐☐

R&D Department, Room 13, Manor House, The John Radcliffe Hospital
Oxford, OX3 9DZ
Tel: 01865 222143 Fax: 01865 222648

- *Please complete by filling in the grey boxes electronically, printing out and signing and then fax within **one working day** of awareness to **01865 222648**. Please note that there are drop down boxes with options you can select.*
- *Refer to the SAE Reporting Form Completion Guidelines for guidance. If you would like to fill it out by hand, please refer to the completion guidelines for options listed in the drop down boxes.*
- *The original should be filed in the Trial Master file. Please ensure that the event is recorded in patient hospital notes and case report form where applicable.*
- *For confidentiality reasons please **DO NOT** save the electronic version of the completed form.*

1. Summary

Report type
Criteria for definition of SAE
Chief Investigator's name
Study number
Date of SAE awareness
Start date of SAE
Stop date of SAE or state if ongoing
Keywords *(SAE Diagnosis or main symptoms)*
Subject initials
Subject ID

2. Narrative

Please provide an account of the event, similar in format to that of a discharge summary. Mention any relevant lab data or diagnostic tests.

3. Evaluation of Event

Outcome
Severity
Action taken with study drug
Other action:
Withdrawn due to SAE? ***Yes/No***

4. Subject Details

Subject DOB
Age
Sex
Height
Weight

SAE No (for office use only): ☐☐☐

5. Suspect Drug(s)

Suspect Drug 1

Drug
Route
Dose details
Indication
Batch number
Expiry date
Start date of drug
Stop date or state if ongoing
If stopped/ lowered dose, did the event resolve after this? ***Yes/No/NA***
If reintroduced did event reappear? ***Yes/No/NA***

Suspect Drug 2 ***(if applicable)***

Drug
Route
Dose details
Indication
Batch number
Expiry date
Start date of drug
Stop date or state if ongoing
If stopped/ lowered dose, did the event resolve after this? ***Yes/No/NA***
If reintroduced did event reappear? ***Yes/No/NA***

Attach supplemental pages if there are more than 2 suspect drugs

6. Death Details ***(if patient died)***

Date of death
Cause of death
Cause of death obtained from

7. Relevant Medical/Surgical History

No. of medical/surgical history CRF pages attached:
If no CRF pages attached, describe relevant medical history

8. Concomitant Medication

No of concomitant medication CRF pages attached
If no CRF pages attached, describe details of conc meds

9. Study Details

Study title
Protocol version or date
Eudract number
Study Design
If blinded, blind broken? ***Yes/No/NA***
(Consider unblinding if SUSAR)
Is there a trial specific Safety Monitoring Committee for this study? ***Yes/No***

SAE No (for office use only): ☐☐☐

10. Principal Investigator Details ***(site specific, and if different from Chief Investigator)***

Name of PI
Address
Telephone
Fax
Email address

Signature of reporter

Date of signing
Full name
Designation
Contact telephone
Email address

This section is to be completed by a medically qualified investigator

11. Causality and Expectedness

Evaluation of causal relationship with suspect drug 1

Evaluation of causal relationship with suspect drug 2 (if applicable)

If the causal relationship is not clear, please indicate how you came to your decision.

If causal relationship is *"related"*, was this event "*expected"* based on the investigators brochure, summary of product characteristics and/or protocol i.e. is it a Suspected Unexpected Serious Adverse Event (SUSAR) and requires expedited reporting to the Medicine and Healthcare Products Regulatory Agency and Ethics Committee?
Yes/No

Signature of Medically Qualified Investigator

Date of signing
Full name
Designation
Contact telephone
Email address

----------END OF DOCUMENT----------

Appendix 2: NPSA Serious Adverse Event Form

National Patient Safety Agency

National Research Ethics Service

REPORT OF SERIOUS ADVERSE EVENT (SAE)

(For all studies except clinical trials of investigational medicinal products)

The Chief Investigator should report any SAE that is both related to the research procedures and is unexpected. Send the report to the Research Ethics Committee that gave a favourable opinion of the research within 15 days of the CI becoming aware of the event. For further guidance see: *http://www.nres.npsa.nhs.uk/applicants/review/after/safety.htm*.

1. Details of Chief Investigator

Name:	
Address:	
Telephone:	
Email:	
Fax:	

2. Details of study

Full title of study:	
Name of main REC:	
Main REC reference number:	
Research sponsor:	

Sponsor's reference for this report: (if applicable)	

3. Type of event

Please categorise this event, ticking all appropriate options:

Death ☐	Life threatening ☐	Hospitalisation or prolongation of ☐ ing hospitalization
Persistent or significant disability or incapacity ☐	Congenital anomaly or birth defect ☐	Other ☐

4. Circumstances of event

Date of SAE:	
Location:	
Describe the circumstances of the event: *(Attach copy of detailed report if necessary)*	
What is your assessment of the implications, if any, for the safety of study participants and how will these be addressed?	

5. Declaration

Signature of Chief Investigator:	
Print name:	
Date of submission:	

6. Acknowledgement of receipt by main REC (please insert name):

The [ ] Research Ethics Committee acknowledges receipt of the above.

Signed:	
Name:	
Position on REC:	
Date:	

Signed original to be sent back to Chief Investigator (or other person submitting report)
Copy to be kept for information by main REC.

Appendix 3: Serious event definitions

Adverse Event (AE):

An AE or adverse event is:

Any untoward medical occurrence in a patient or clinical investigation participants caused by the device under investigation, which does not necessarily have to have a causal relationship with Device.

An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom or disease temporally associated with the use of the device, whether or not considered related to the device.

Adverse Device Effect (ADE)

All untoward and unintended responses to the medical device.

The phrase "responses to a medical device" means that a causal relationship between the device under investigation and an AE is at least a reasonable possibility, i.e., the relationship cannot be ruled out.

All cases judged by either the reporting medically qualified professional or the sponsor as having a reasonable suspected causal relationship to the device qualifies as a device effect.

This also includes any event resulting from insufficiencies or inadequacies in the instruction for use or deployment of the device and includes any event that is a result of a user error.

Serious Adverse Event (SAE):

SAE is an adverse event that

- Led to death
- Led to foetal distress, foetal death or congenital abnormality or birth defect.
- Led to serious deterioration in the health of the subject that
    - Resulted in a life-threatening illness or injury
      NOTE: The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.
    - Resulted in a permanent impairment of a body structure or a body function

- Required in-patient hospitalisation or prolongation of existing hospitalisation
- Resulted in medical or surgical intervention to prevent permanent impairment to a body structure or a body function
- Other important medical events*
  *Other events that may not result in death, are not life threatening, or do not require hospitalisation, may be considered a serious adverse event when, based upon appropriate medical judgement, the event may jeopardise the patient and may require medical or surgical intervention to prevent one of the outcomes listed above

To ensure no confusion or misunderstanding of the difference between the terms "serious" and "severe", which are not synonymous, the following note of clarification is provided:

The term "severe" is often used to describe the intensity (severity) of a specific event (as in mild, moderate, or severe myocardial infarction); the event itself, however, may be of relatively minor medical significance (such as severe headache). This is not the same as "serious," which is based on patient/event outcome or action criteria usually associated with events that pose a threat to a participant's life or functioning. Seriousness (not severity) serves as a guide for defining regulatory reporting obligations.

Serious Adverse Device Effects (SADE):

A serious adverse device effect (SADE) is any untoward medical occurrence seen in a patient that can be attributed wholly or partly to the device which resulted in any of the characteristics or led to a characteristics of a Serious adverse event.

SADE is also any event that may have led to these consequences if suitable action had not been taken or intervention had not been made or if circumstances has been less opportune.

All cases judged by either the reporting medically qualified professional or the sponsor.

Unanticipated Adverse Device Effect (UADE):

Any serious adverse device effect on health or safety or any life-threatening problem or death caused by, or associated with a device, if that effect, problem, or death was not previously identified in nature, severity or degree of incidence in the investigational plan or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that related to the rights, safety or welfare of the subject.

Oxford University Hospitals NHS
NHS Trust

Kadoorie Centre
The John Radcliffe
Headley Way
Headington
Oxford
OX3 9DU

Telephone: 01865 228979
Fax: 01865 857611
Email: calms.trial@nda.ox.ac.uk

PATIENT INFORMATION SHEET – CALMS-2 STUDY
(Computer ALerting Monitoring Surgical patients study)

Leeds (West) REC Ref: 11/YH/0056

A study to determine if medical observations are best taken continuously or intermittently, and whether an "intelligent" machine can help doctors and nurses interpret them. (Phase 4)

PART ONE – INVITATION TO JOIN THE CALMS-2 STUDY

You are being invited to take part in a research study. Before you decide it is important for you to understand why the research is being done and what it would involve. You should understand enough about its risks and benefits to be able to make an informed decision. This process is known as informed consent. Please take time to read the following information carefully and discuss it with others if you wish. Ask if there is anything that is not clear or if you would like more information. Take time to decide whether or not you wish to take part, and thank you for reading this sheet.

What is the purpose of the study?

After patients have had surgery, all patients have measurements taken of their pulse, blood pressure, breathing rate, temperature and the body's oxygen levels. This can be done by hand by a nurse or automatically by a machine called a monitor. It isn't clear whether it is better to take these measurements by hand at certain times or by machine all the time. It is also unknown whether the monitors hospitals currently use

could be improved to provide better information for the doctors and nurses caring for patients.

We want to test whether current monitors are helpful, and if a new attachment called the ‘Software Monitor’ makes them more reliable and useful to medical staff. The Software Monitor is based on new computer technology developed in Oxford. If the Software Monitor proves to be successful it could improve both nurses’ and doctors’ abilities to watch over patients. It could also alert them earlier to a patient who may be in need of more treatment, a different type of care, or more or less monitoring.

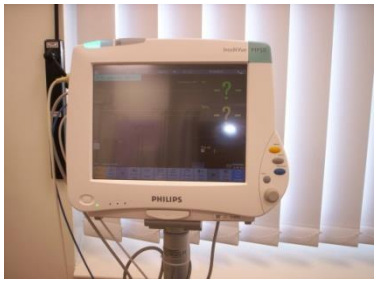
Why have I been chosen?

This study has been designed to monitor only patients that have had surgery on their gastrointestinal system (digestive system). Therefore we are asking all patients scheduled to have this type of surgery if they would be happy to take part.

Do I have to take part?

Patients undergoing surgery on their upper gastro intestinal system are needed to take part in the study. However it is up to you to decide whether or not to take part. If you do decide to take part you will be given this information sheet to keep and be asked to sign a consent form, and you would be free to withdraw at any time and without giving a reason. A decision to withdraw at any time, or a decision not to take part, would not affect the standard of care you receive.

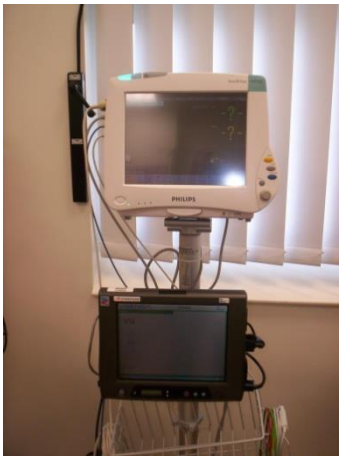
What will happen to me if I take part?



For patients who agree to enter the study, their care or surgery will not change. All patients on returning to the surgical ward after an operation are placed into beds that have standard hospital monitors that measure

heart rate, blood pressure, temperature, and oxygen in the blood. The picture opposite shows a standard hospital monitor.

For those that agree to take part in this study, there would be an extra monitor – the 'Software Monitor' attached to the hospital monitor. A picture of this is shown below.



The 'Software Monitor' would continuously record what the monitor is displaying and would give the nurses and doctors a number that will be an extra measurement that nurses and doctors will take into account when they are seeing how well you are doing. When you are starting to feel better and wanting to get out of bed, a mini monitor would then be attached to you to allow you to get around, and a computer would also record what the mini monitor is measuring without the need for any wires. To allow the information from your monitors to be reviewed by nursing staff when they are not at your bedside, the information will be displayed on a screen on the ward, (along with your name to allow identification). A research nurse would also come and look at your notes whilst you are in the study and would check that the computer is recording your measurements.

You would wear the monitor for the duration of your hospital stay. When your surgical doctors are happy that you are well enough to go home, you would then be disconnected from the monitor and your time in the study would end.

If, after reading Part One, the study sounds like something you might agree to taking part in, you may find it helpful to read the further information in Part Two before you make your decision.

PART TWO – ADDITIONAL INFORMATION ABOUT THE CALMS-2 STUDY

Who is organising and funding the research?

Members of the intensive care and upper gastrointestinal surgeons within the Oxford Radcliffe Hospital NHS Trust are organising this research.

The Oxford Partnership Comprehensive Biomedical Research Centre, a centre given grants by the Government to improve patient health is funding this research.

Who has approved the study?

Any research conducted on patients has to be first approved by an NHS Research Ethics Committee (REC). RECs look after the rights, well being and dignity of patients. This study has been reviewed by the Leeds (West) REC and given a favourable opinion and the reference 11/YH/0056.

Is there a contact point where I can seek independent advice about participating in this study?

Yes, the hospitals Patient Advice and Liaison Service (PALS) Office.

Are there any risks?

There are no known risks to this study as the only thing that differs from the care that you would receive if not in the study if that a computer – the 'Software Monitor' will be continuously recording what your hospital monitor is showing.

What if something goes wrong?

This study is investigating the addition of a computer – the 'Software Monitor' to existing hospital monitors rather than new monitors. Monitors are used on virtually all wards. NHS bodies are legally liable for the negligent acts and omissions of their employees. If you are harmed whilst taking part in a clinical trial as a result of negligence on the part of a member of the study team this liability cover would apply.

Non-negligent harm is not covered by the NHS indemnity scheme. The Oxford Radcliffe NHS Trust, therefore, cannot agree in advance to pay compensation in these circumstances. In exceptional circumstances an ex-gratia payment may be offered.

What are the possible benefits of taking part?

There may be a clinical benefit to you from taking part in this study, it is hoped in the longer term that this study will contribute to improved standards of care received by surgical patients in the future, based on the information we record on you and your stay. Participants in this study would be monitored on the surgical wards until their doctors say they are well and ready to be discharged. Although participants may be connected to a monitor for longer than normal, the equipment can be made portable so that a participant can move about.

Would my taking part in this study be kept confidential?

Information gathered from the monitors will be displayed on a computer screen on the ward. Your name will be included in this display to enable the nurses to use this information whilst caring for you.

All information which would be collected about participants during the course of the study would be kept strictly confidential and would include information such as the data recorded by the 'Software monitor'. The study will find out if patient monitors are helpful, and if they could be improved. All data collected would be "anonymised"- that is, any information that leaves the hospital would have all names and address removed. Individuals could not be recognised from it. Anonymised data may be made available to other groups for the purposes of improving clinical diagnosis and treatment.

What happens if I have any questions, concerns or complaints about the study?

If you have any questions concerning the study, please ask the person presenting this form to you, or contact Drs Watkinson or Salmon, the Research Doctors on 01865 857626, or by writing to Drs Watkinson or Salmon, Kadoorie Centre, Level 3, John Radcliffe Hospital, Headley Way, Headington, OX3 9DU.

What if I wish to complain?

If you have any comments, concerns or complaints about any aspect of the way you have been approached or treated during the course of this study, you should write to Dr Peter Watkinson, Kadoorie Centre, John Radcliffe Hospital, Headley Way, Headington, Oxford, OX3 9DU.

Where can I find the results of the study?

The results are estimated to be published in 2012. If you would like a copy, please contact the Chief Investigator.