STUDY SHORT NAME:

DCD 10-10 (Pilot Study):

Trial of a breathing test to predict time of circulatory death in organ donation candidates (a safety and feasibility study)

FULL TITLE:

DCD 10-10 (PILOT STUDY): VALIDATION OF A SPONTANEOUS BREATHING TEST TO BETTER PREDICT TIME TO CIRCULATORY DEATH IN ORGAN DONATION CANDIDATES (A SAFETY AND FEASIBILITY STUDY)

Protocol Number: 1

Clinical Trial Protocol Amendment Number:**4**

Version Number: **5**

Universal Trial Number: U1111-1197-5673

Date: **09/03/2018**

STATEMENT OF COMPLIANCE

This Document is a protocol for a clinical research study. The study will be conducted in compliance with all stipulations of this protocol, the conditions of ethics committee approval, the NHMRC National Statement on Ethical Conduct in Human Research (2007)

and the Note for Guidance on Good Clinical Practice (CPMP/ICH-135/95) annotated with Therapeutic Goods Administration comments.

Contents

1. PROTOCOL SYNOPSIS

Title	DCD 10-10 (Pilot Study): Validation of a spontaneous breathing test to better predict time to circulatory death in organ donation candidates (A safety and feasibility study)
Short Title	DCD 10-10 (Pilot Study)
Objectives	This study aims to establish a simple, safe, bedside test to better assess respiratory drive, and hence probability of rapid death, in patients eligible for donation after circulatory death (DCD). Our objective is to improve correct prediction of death within 90 minutes by greater than 10%.
Design	A multicenter prospective observational pilot trial
Outcomes	*Primary* 1. To assess the feasibility and safety of performing a spontaneous breathing trial on a T-piece humidification system for 10 minutes in patients eligible for DCD *Secondary* 1. To obtain descriptive statistics for the sensitivity and specificity of the test in predicting patient death within 90 minutes 2. Comparison of the sensitivity and specificity of the DCD 10-10 test with staff specialist opinion regarding predicted time to death. 3. Predictive value of other patient variables, including BMI, ionotrope/vasopressor requirement and use of sedative and analgesic agents.
Interventions	The DCD 10- 10 test is a spontaneous breathing trial on a T-piece humidification system performed at the bedside by the treating Staff Specialist. A positive test result will be recorded if patient oxygen saturations decrease by 10%, or respiratory rate is less than 10. If this does not occur after a 10 minute period, the patient will be reconnected to the ventilator with a negative test result recorded.
Sample Size	70 patients
Population	Patients consented for organ donation after circulatory death.
Eligibility Criteria	*Inclusion Criteria* - All patients who meet the GIVE trigger and have consented for DCD organ donation will be eligible for inclusion in the trial. Therefore, inclusion criteria will include patients whom are mechanically ventilated, with a Glasgow Coma Scale Score < 5, in whom end of life conversations have taken place.

	Exclusion Criteria - Patients less than 18 years of age - Patients who are pregnant - Non-ventilated patients - Patients meeting the criterial for brain death - Patients screened by the organ donation team, but deemed to be inappropriate for DCD, or whereby the person responsible has not given consent for DCD to proceed - Inability to gain consent for study enrolment <u>Note</u>: Patient's receiving a high level of respiratory support (FiO2 > 60%, PEEP > 10) or haemodynamic support (combined vasopressor/ ionotrope requirement > 1microg/kg/min) will be eligible for enrolment in the study and will have all data collected, including Staff Specialist prediction of time to death. It will then be at the Staff Specialists discretion as to whether the DCD 10 – 10 test is necessary to perform.
Study Duration	Patient recruitment is estimated to take 6 months to 1 year based on current rates of DCD at the participating sites.

2. GLOSSARY OF ABBREVIATIONS & TERMS

DCD	Donation after Circulatory Death
Intended donor	A donor consented for DCD donation who does not die within the required time frame for organ donation and therefore does not undergo organ retrieval.
WCRS	Withdrawal of cardiorespiratory support
ETT	Endotracheal Tube
RedCap	'Research Electronic Data Capture'. A trade name online data collection system.
FiO2	Fraction of inspired oxygen concentration
PEEP	Positive End Expiratory Pressure
HMRI	Hunter Medical Research Institute
ANZICS	Australian New Zealand Intensive Care Society
ODC	Organ Donation Coordinator

3. ADMINISTRATIVE INFORMATION

3.1. Chief Investigator

Name: Dr Adelaide Charlton
Titles: BMed, Dip Child Health, MMed (Critical Care)
Address: John Hunter Hospital, Lookout Road New Lambton, 2305 NSW
Tel: 02-49214255
Email: dcd1010study@gmail.com

3.2. Coordinating Centre

John Hunter Hospital, Newcastle NSW 2305

3.3. Management Committee

Dr Adelaide Charlton (Chief Investigator)
Dr Jorge Brieva (Principle Investigator and study supervisor)
Ms Nicole Coleman (Associate Investigator)
Ms Susan Frew (Associate Investigator)
Mr Adrian Watson (Associate Investigator)

3.4. Funding

John Hunter Hospital Charitable Trust Grant of $20 000.00
Funds have been allocated as follows:

- Computer Programming with the RedCap online data collection system: $5000.00
- Statistical Analysis by the Hunter Medical Research Institute (HMRI): $8 000.00
- Travel Expenses: $1500.00
- Subsidization of Organ Donation Coordinator/ Staff Specialist time: $100 x 60 patients = $6000
- Stationary: $500.00

If additional funding is required for travel expenses or subsidization of Organ Donation Coordinator time, a research grant will be sought from Organ Donation Australia.

3.5. Trial Registration

The trial is registered with the Australian and New Zealand Clinical Trials Register (request number: 373091)

4. BACKGROUND INFORMATION

Donation after Circulatory Death (DCD) is now a well-established pathway to organ donation. In 2016, 503 organ donation events occurred in Australia, with 128 of these via the DCD pathway, representing 25% of all organ donations (1). This reflects international figures, with DCD comprising a significant proportion of total donations (2). Furthermore, DCD represents a rapidly expanding area of organ donation, with numbers of successful donors having doubled since 2009 (1). The reason for this is likely multifactorial, with more policy and guidelines available (2, 3, 4), better reported graft and recipient outcomes (5) and better healthcare worker and community education (6).

One of the most important variables to consider for DCD is likelihood of circulatory arrest within the required timeframe. This is organ specific, and necessary to minimize prolonged warm ischemia times. Currently in Australia, the Intensive Care Specialist must inform state agencies of the likelihood of death occurring within 90 minutes of cessation of cardiorespiratory support, to activate an organ procurement team.

Two possible outcomes are associated with an incorrect prediction of time to death. Either the procurement team is not activated, and a missed opportunity arises, or organ procurement team activation occurs, but death is beyond a timeframe for acceptable organ warm ischaemic time. This results in 'intended' donors, patients who are consented for DCD, but who are unable to undergo organ donation. These intended donors not only place a significant cost burden on the healthcare system, but also add to the burden faced by families, who are often troubled by the inability to fulfill their loved ones wishes and who may then see the donation process as a failure. Furthermore, the question arises as to the humanity of maintaining a person on life support for extended periods of time to allow organization of a donation process that may not eventuate. This is a concept that is not only difficult for family, but can be challenging for staff caring for the patient to come to terms with, particularly if the patient is unstable and requiring a lot of support.

The current incidence of intended donation in Australia is growing along with the rate of increased DCD candidates, having been reported at 91 in 2014, 129 in 2015, and 143 in 2016. Last year in Australia, the amount of DCD intended donors ranged from 27 – 34% by jurisdiction. Inability to accurately predict death within 90 minutes was the most common reason organ procurement did not proceed (1).

Several literature reports of variables improving prediction of time to death include scoring of cardiovascular, respiratory, metabolic and neurologic parameters (10, 11, 12,

13, 14, 15). Based on previous research, the Intensive Care Specialist should be able to correctly predict death within 60 minutes in approximately 80% of cases (7, 8, 9). However, current data from NSW and National reports, suggest a figure closer to 60% (1).

Two previously reported tools (16, 17) have included a temporary disconnection from mechanical ventilation to assess the spontaneous respiratory drive and decline in oxygenation. These tools are reported to have prediction rates of over 80% when used alone and up to 88% when used in conjunction with other clinical predictor variables (17). No study to date has looked at whether addition of one of these tools to current methods improves prediction accuracy.

It is recommended practice within Intensive Care medicine to use spontaneous breathing trials to assess a patient's respiratory drive and ability to be weaned from a ventilator (18). In patients undergoing donation after brain death (DBD) donation an apnoea test is performed to assess respiratory effort (19). At present, in Australia, a spontaneous breathing trial is not routinely used in DCD donation. Therefore, prior to assessing this as a tool to predict time to death in DCD patients, it would be important to establish the practicalities and safety of performing such as test.

4. STUDY OBJECTIVES

4.1. Primary Objective

To establish a simple, safe, bedside test to better assess respiratory drive, and hence probability of rapid death, in patients eligible for donation after circulatory death (DCD). Our objective is to improve correct prediction of death within 90 minutes by greater than 10%.

4.2. Secondary Objectives

Secondary objectives are to collect data on other potential predictors of rapid death, including patient demographics, medical history, level of respiratory and cardiovascular support and infusions of sedative and analgesic agents. Accuracy of Staff Specialist prediction based on these variables will also be investigated.

5. STUDY DESIGN

This is a prospective observational multicenter pilot study.

It will be performed at 7 tertiary Australian hospitals:

- The John Hunter Hospital, Newcastle NSW

- The Royal Prince Alfred Hospital, Sydney NSW
- The Royal North Shore Hospital, Sydney NSW
- The Royal Brisbane Hospital, Brisbane QLD
- The Cairns Hospital, QLD
- The Tweed Hospital, QLD
- The Royal Melbourne Hospital, Melbourne VIC
- The Royal Adelaide Hospital, SA
- Flinders Medical Centre, SA
- The Lyell McEwan Hospital, SA

6. STUDY OUTCOMES

6.1. Primary Outcomes

To assess the safety and feasibility of performing the DCD 10-10 test, a spontaneous breathing trial on a T-piece humidification system for 10 minutes in patients eligible for DCD.

6.2. Secondary Outcomes

1. To obtain descriptive statistics for the sensitivity and specificity of the test in predicting patient death within 90 minutes
2. Comparison of the sensitivity and specificity of the DCD 10-10 test with staff specialist opinion regarding predicted time to death.
3. To obtain descriptive statistics for the predictive value of other, previously studied, patient variables. These include BMI, respiratory support, ionotrope/vasopressor requirement, and use of sedative and analgesic agents
4. To assess the family acceptability of performing ante-mortem research in the context of organ donation. This will be done by a direct measure of consent rate.

Note: In this pilot study, the DCD 10-10 test will be performed just prior to withdrawal of cardiorespiratory support (WCRS), with the organ procurement team on site. This will ensure that if adverse events, such as cardiorespiratory instability or arrest occur, organ donation can proceed as planned. If this study proves the intervention is safe, a larger study will be performed. This will be appropriately powered to evaluate the sensitivity and specificity of the test when conducted at the time of DCD patient recruitment, as would be its intended use.

7. STUDY POPULATION

7.1. Inclusion Criteria

All patients who meet the GIVE trigger for DCD organ donation will be eligible for inclusion in the trial. Therefore, inclusion criterial will include patients whom are mechanically ventilated, with a Glasgow Coma Scale Score < 5, in whom end of life conversations have taken place. Prior to discussion of study consent, family should have consented for the DCD process and the site organ donation team should have performed their initial patient screening and family discussions.

7.2. Exclusion Criteria

The following patients will be excluded from study enrollment:

- Patients less than 18 years of age
- Patients who are pregnant
- Non-ventilated patients
- Patients meeting the criterial for brain death
- Patients screened by the organ donation team, but deemed to be inappropriate for DCD, or whereby the person responsible has not given consent for DCD to proceed
- Inability to gain consent for study enrolment

8. STUDY METHODS

8.1. Informed Consent

Informed consent will be obtained from the person responsible. This should be the same person whom has been legally appointed to provide consent for the DCD process.

The Organ Donation Coordinator (ODC) has been chosen as the person best equipped to provide information about the study and obtain consent. The ODC is fully trained in family discussions and are able to put family in contact with the usual support services for families undergoing the donation process (e.g. the Donor Family Support Service).

It is acknowledged that decisions regarding organ donation can place a large amount of strain on families at a difficult emotional time. In order to avoid consent fatigue a number of steps will be taken.

- Firstly, the research study will be introduced by the ODC during a private meeting immediately after DCD consent has been obtained.
- The family and the person responsible should be given the option to either receive the information at that time, schedule another meeting to discuss the study information or not to receive any further information about the study.
- The ODC should be responsible for obtaining consent, regardless of the decided time for discussion. This should be in line with the standard operating procedures for organ donation consent (see attached copy of the policy directive

for 'Deceased Organ and Tissue Donation – Consent and Other Procedural Requirements').

An example of a sample dialogue for consent:
"We are trying to improve successful organ donations in Australia. One way of doing this is to see how someone breathes for themselves without the ventilator. We believe this may give us a better idea of whether death will occur quickly once life support is taken away. If death does not occur quickly, the organs are without enough blood and oxygen supply for too long and they cannot be transplanted. If you would like to hear more about a study we are doing on this we could discuss it now, otherwise we could meet again in 1 -2 hours to go over the information. If you believe your loved one would not want to be part of a study, we will not discuss this any further. Regardless of your decision our priority is ensuring that all usual procedures for organ donation are carried out to ensure the best chance of successful transplantation"

A record will be kept off all patients consented for DCD organ donation and whether they were consented for DCD 10-10 study, refused consent or were not asked. The rate of consent will stand as a surrogate measure for family acceptance of participation in research during the organ donation process. Other methods of analyzing family response, such as surveys or follow up phone calls were considered, but dismissed due to the potential to contribute to information overload and contribute to family distress.

8.2. Data Collection

Consented patients will undergo assessment using the RedCap online data collection form (See Appendix 1). This online platform case report form is password protected and the information uploaded encrypted.

Independent predictor variables will be collected following study enrolment. These include:

- Patient age
- Weight
- Admission diagnosis
- Apache II severity score and history of chronic cardiorespiratory illness
- Days on mechanical ventilation
- Assessment of airway difficulty and anatomy

Well established clinical predictor variables (10, 11, 12, 13, 14, 15) for death within 90 minutes will be also be entered into the RedCap system. These should be entered within 1 hour prior to performing the DCD 10-10 test and include:

- Haemodynamic parameters: Blood pressure, heart rate, urine output, presence dose of vasopressors, ionotropes
- Ventilator settings: Ventilator mode, FiO2, oxygen saturations, PEEP, tidal volume, PaCO2
- Best neurological response: GCS, pupillary response
- Sedation and analgesia treatments: Cumulative dose during the 12 hours prior to WCRS.
- Laboratory results including lactate, pH and glucose.

8.3. Record of Staff Specialist Opinion

Upon patient enrolment, prior to performing the DCD 10-10 test, the treating Staff Specialist will be asked to enter their personal prediction of time to death. They will be able to select from the following options: 30 minutes, 60 minutes, 90 minutes or greater than 90 minutes. Once this estimation has been recorded on the Redcap system, the page will be locked and no alteration to the prediction will be possible.

8.4. Administration of the DCD 10-10 test

The DCD 10–10 test will be performed immediately prior to planned WCRS. It is intended that the surgical organ procurement team will be on site with all necessary steps for DCD, prior to WCRS, completed.

The DCD 10-10 test will be performed by the treating Staff Specialist or most senior registrar, if the Staff Specialist is not on site. Prior to commencing the test, patient ventilator settings and inspired oxygen fraction will be maintained whilst the endotracheal tube (ETT) is suctioned. Respiratory rate, pattern and oxygen saturation level will be recorded prior to commencing the test. The ETT will then be connected to a T-piece breathing humidified room air. Upon connection a stop-watch for 10 minutes will be set. The patient will be reconnected to the ventilator if, at any point, respiratory rate is less than 10, the patient has an apnoea of more than 10 seconds or oxygen saturation fall by 10% of baseline, the patient will be transferred back to the ventilator at their original settings. If these criteria are met, a positive test result will be recorded. If these criteria are not met after 10 minutes, the patient will be reconnected to the ventilator and a negative test result recorded.

All intravenous infusions and other treatment measures will be continued during the test. Bedside nurses and clinicians are able to give sedation and analgesia, as per their usual practice, if deemed necessary during the 10-10 test to ensure patient comfort and prevent endotracheal tube dislodgement.

Clinicians will have the opportunity to record any changes in patient condition after performing the test. These may include inability to restore initial ventilator settings, recruitment and oxygenation, altered respiratory or haemodynamic parameters once transferred back to the ventilator or cardiac arrest during evaluation. Observed

adverse associations with the test will then form the basis of secondary outcomes to be investigated further in the larger trial.

Time of WCRS and time of death will be recorded on the RedCap data collection system. These variables will be entered by the Organ Donation Coordinator, who is independent of the 10-10 intervention. Time of death will be checked off the patient notes and the patient death certificate.

8.5. Precautions and Adverse Reactions

Patients receiving a high level of respiratory support (FiO2 > 60%, PEEP > 10) or haemodynamic support (combined vasopressor/ ionotrope requirement > 1microg/kg/min) will be eligible for enrolment in the study. In these patients, however, it will be left to the treating Staff Specialist's discretion as to whether or not it is too higher risk to perform the DCD 10-10 test. In those patients whereby the decision is made not to perform the intervention, all other data will be collected, including Staff Specialist prediction of time to death. These patients will still be included in data analysis. It is expected that, given the usual nature of illness leading to eligibility for organ donation, the number of patients that meet this criteria will be few. It is also expected that for this group of unstable patients, correct staff specialist prediction, based on previously documented patient variables alone, will be more likely. These projections will be assessed on data-analysis.

In this safety and feasibility study, the DCD 10-10 test will be performed just prior to planned WCRS. It is intended that the surgical organ procurement team will be on site and all steps necessary for DCD prior to WCRS will have taken place. At the time of ventilator disconnection for the DCD 10-10 test, the organ donation coordinator will commence the stop-watch for warm ischaemic time. In this way, in the unlikely event of patient cardiac arrest during the DCD 10-10 test, organ procurement will still continue as planned, eliminating any risk that the organ donation opportunity will be lost. After the DCD 10-10 intervention and ventilator reconnection, the final WCRS can be performed as per usual organ donation procedure at the discretion of the treating team and Organ Donation Coordinator.

8.6. Withdrawal of Consent

The Person Responsible has the right to revoke consent for patient participation in the study at any time. Similarly, the Person Responsible has the ability to withdraw consent to pursue organ donation prior to organ retrieval. In this event, data collection will be ceased immediately. Family will be asked whether data collected up until the point of withdrawal can be used in the final data analysis. If the decision is to withdraw from the study completely, all the information collected from and about the patient will be removed from the study and existing data destroyed. If final data analysis has already occurred, however, with data anonymously included in the study database, the person responsible will be made aware that complete data erasure is not possible.

9. STUDY ASSESSMENTS

9.1.Screening

All patients consented for DCD will be screen for eligibility in the study and consent requested for participation.

9.2.Baseline

Baseline characteristics for all patients will be collected in the demographics section of the online database.

9.3.Follow up

Patients will be followed up in the hours immediately following the DCD 10-10 test, until death occurs, whereby time of death will be recorded and remaining data, including the total quantity of vasopressor, ionotrope, sedative and analgesic infusions will be calculated.

It is unlikely that any patient will be lost to follow up, given the ongoing presence of the organ donation coordinator involved in the study enrolment, data collection and study intervention. If however, any patients are lost to follow up, patient re-identification will enable the time of death and quantity of drug infusions to be recorded retrospectively from the death certificate and the patient records.

9.4.Record Retention

All information will be kept in accordance with the Good Clinical Practice Guidelines, unless advised otherwise by regulatory authorities. It is anticipated that data from this study will be stored on a password protected online database for 15 years after completion.

10. SAFETY MONITORING AND REPORTING

10.1. Adverse Outcomes (ADO)

The potential ADOs identified are surrounding inability or difficulty restoring initial patient parameters following the DCD 10-10 test. These include:

- Hypotension – requiring increased vasopressor or ionotropic support
- Arrhythmias – requiring anti-arrhythmic agents or increased haemodynamic support
- Lung derecruitment – requiring increased PEEP, recruitment manouvers or increased FiO2

To minimize these risks, Staff Specialists can elect not to perform the DCD 10-10 test in patients who meet criteria for a high level of cardiorespiratory support. This includes patients who are on a PEEP > 10, FiO2 > 60 or total vasopressor/ ionotrope infusion > 1microg/kg/min.

There are potential risks of harm to the patient family. Performing research on the patient may add further information to an already complex situation. It is also possible that the family may suffer consent fatigue or receive mixed messages about the meaning of the test. In an attempt to reduce this, the family will be given the option of whether or not they want to receive information about the study and when

they wish for this to happen. They will also receive an information sheet detailing the meaning of the test. They will receive support from the Intensive Care social worker and the organ donation support service, as is usual practice in organ donation. A secondary outcome of the study is to assess whether being involved in the research in the setting of organ donation is acceptable to families. If it is unacceptable, with consent rates less than 50%, this will need to be addressed prior to planning any larger studies.

10.2. Serious Adverse Outcomes (SADOs)

There is a theoretical risk of cardiac arrest during or shortly after the DCD 10-10 test. It is because of this risk that a pilot study is being performed prior to a larger study powered to test the sensitivity and specificity of the DCD 10-10 test in predicting time to death in DCD patients. This pilot study aims to assess the risk of SAOs

10.3. Suspected Unexpected Serious Adverse Outcomes (SUSAOs)

There is a theoretical risk of lost donation opportunity. This SUSAO is unexpected, as all possible measures have been put in place to enable immediate organ retrieval should death occur during the DCD 10-10 test. It is therefore not believed that the DCD 10-10 test will alter organ warm ischaemic time.

10.4. Study Termination

The study, in its current format, will be terminated prematurely in the event that there are 2 reported cases of cardiorespiratory arrest during the DCD 10-10 test. This would equate to a cardiac arrest prevalence of 2.8%.

In addition, the study will be terminated immediately if there are any reports of inability to proceed with organ donation as a direct result of the DCD 10-10 test.

Interim analysis will assess for other adverse events, such as failure to restore haemodynamics, or previous ventilator settings without intervention. If these are seen to occur with a rate of greater than 10%, the nature of the adverse outcomes will be reviewed, with the study ceased if the intervention deemed to be too higher risk.

11. CONSENT & ETHICAL CONSIDERATIONS

11.1. Ethical Conduct of the Study

All participating study investigators will have completed Good Clinical Practice (GCP) training, with evidence of certification received by the Chief Investigator.

All study investigators will be assessed for conflicts of interest. At present there are no for-seen financial conflicts of interest.

There are no for-seen commercialisation or intellectual property implications of the funding arrangement with the John Hunter Charitable Trust Foundation. The Charitable Trust has no pecuniary interests in the outcome of the study.

Common law supports medical decisions that take into account the interests of the patient, even if the patient is no longer conscious or able to participate in decision-making. If those best interests, either previously expressed by the person, or purported to be their best interests as expressed by the person responsible include the fact that the person would wish to donate their organs in the best possible condition to suitable recipients, then it is implicit that the person would wish those organs to be retrieved and transplanted in the best possible condition in order to benefit the recipient. It would therefore be in the person's best interests to undergo any ante-mortem interventions that would optimize the condition of the organs for transplantation whilst not causing suffering to the patient or to the patient's family (21). If ante mortem procedures are withheld because they are of no immediate medical benefit to the patient, there may be a breach of a duty of care to the patient concerning consideration of the patient's best interests, including the provision of the patient's organs in the best possible condition for transplantation.

A preliminary statement (not yet published) regarding the ethical and legal positions of The Australian New Zealand Intensive Care Society (ANZICS) endorses ante-mortem procedures that occur solely for the purpose of organ donation. This includes delaying WCRS, commencing or continuing medical supports and performing investigations. Therefore, performing the DCD 10-10 test on these patients, an intervention with the aim of investigating respiratory drive and optimising organ donation procedures in Australia can be ethically justified.

In relation to potential harms to the patient, ANZICS states that ante-mortem procedures should be performed so long as there is no risk of harm to the patient or their family, but acknowledges that defining harm for each individual patient is complex, stating that it should take into account the clinical circumstances and view of the person responsible on behalf of the patient. In obtaining informed consent to proceed with the DCD 10-10 test and taking all possible precautions to minimise risk, this study is being performed in alignment with the current ANZICS position.

11.2. Human Research Ethics Committee Review

Ethics approval for this study will besought from the Hunter New England Clinical Research Ethics Committee (HREC). A separate Site Specific Application (SSA) will be submitted for additional centres, with the research proposal sent the North Sydney Local Health District, Melbourne Health, the Royal Brisbane and Women's Hospital HREC and the Sydney Local Health District Ethics Review Committee.

11.3. Informed Consent Procedures

Consent will be obtained from the Person responsible according to the NSW Guardianship Act 1987. This will be the same person who has consented for DCD to proceed. An information brochure will be provided for the Person Responsible, patient family, detailing the background of the study, data collection and intervention. It will also address issues of confidentiality, security, possible adverse events and withdrawal of consent. Consent will be obtained by either the treating Staff Specialist or the Organ Donation Coordinator for each site.

11.4. Confidentiality and Privacy

Upon enrolment, the participant will be assigned a unique, coded study number, to be used for the duration of the trial. All data will be collected on the secure password locked RedCap online data collection system. Re-identification will only occur if necessary to verify collected data or enable thorough investigation of an adverse event. Only the Associate Investigator and the Organ Donation Co-ordinators at each site will have password access to the RedCap system, ensuring that all collected data is secure. Any Information collected from the participant will be recorded in the patient's medical record.

12. STATISTICAL METHODS

12.1. Sample Size Estimation

In order to detect adverse events with a prevalence of 5% (using a 95% confidence interval), it is calculated that this study will require recruitment of 59 participants for the DCD 10-10 test (21).

Due to the possibility that some enrolled patients, on a high level of cardiorespiratory support, may be excluded from the DCD 10-10 intervention (see section 9.4). Therefore, study recruitment will continue until at least 60 patients have been enrolled who actually receive the DCD 10-10 test. We estimate that the total number of patients enrolled in the study will approximately 70 patients.

12.2. Statistical Analyses Plan

Positive and negative predictive value will be calculated by a statistician from the Hunter Medical Research Institute. This statistician will be independent of the data collection process. A logistic regression will analyse death within 90 minutes as the outcome (dichotomous) against positive test result (dichotomous).

A multivariate logistic regression will be used to adjust for potential confounders, e.g. comorbidity, age, etc. The model fit will be measured using the area under the receiver operating characteristic (ROC) curve and the increase in area under the curve (AUC) on addition of the 10-10 test will be measured.

Consent rate will be calculated as a direct percentage of total patient families asked to participate in the study.

12.3. Interim Analyses

Interim analysis will be performed after 10, 25 and 50 patients have been recruited. This will be performed by the Chief Investigator and the HMRI statistician

13. QUALITY ASSURANCE

All study investigators have provided record of completion of Good Clinical Practice Training. They have also provided a curriculum vitae outlining their appropriate qualifications and specific training in organ donation.

14. PUBLICATIONS AND REPORT

Based on current DCD consent rates at each of the participating sites, patient recruitment and data collection is expected to take one year.

Results will be written up and submitted to the College of Intensive Care Medicine as a trainee formal project. An application for publication in the Journal of Critical Care Medicine will also be made.

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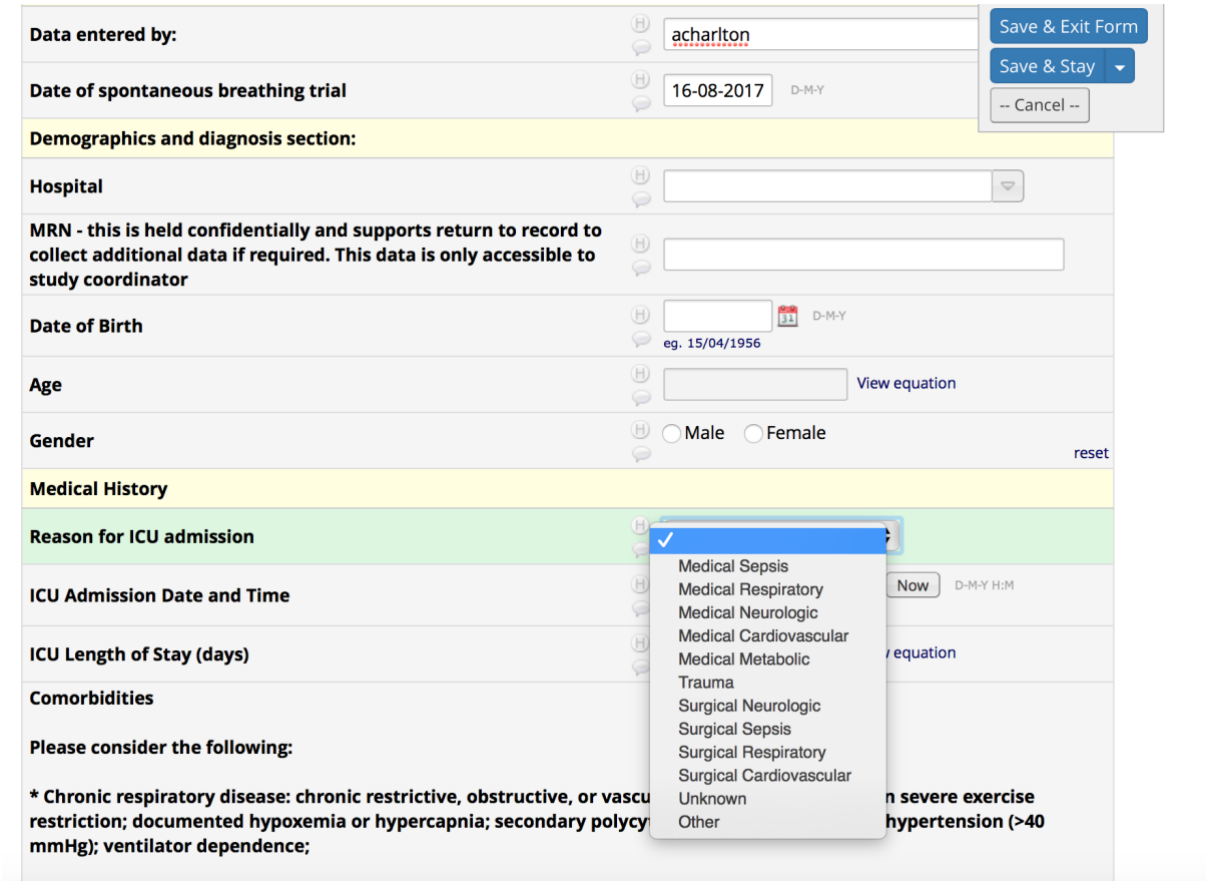
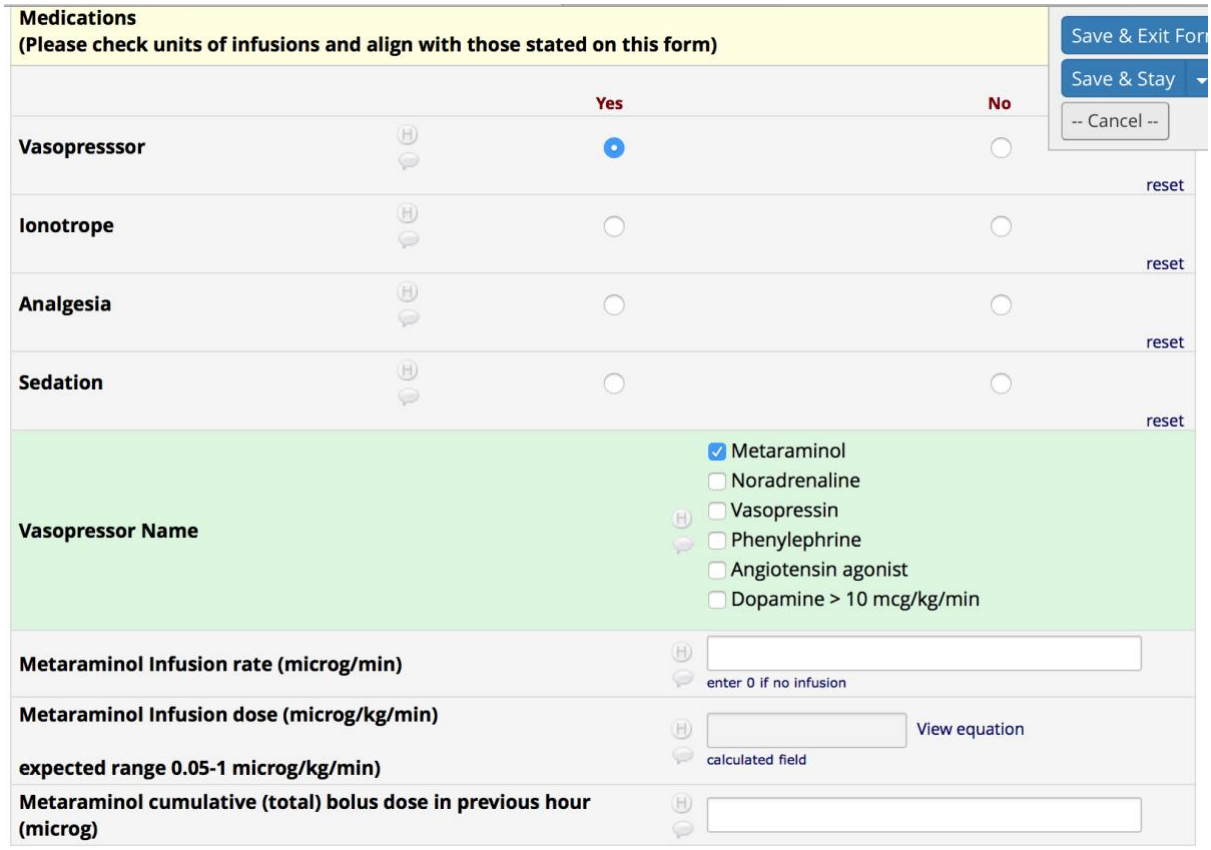
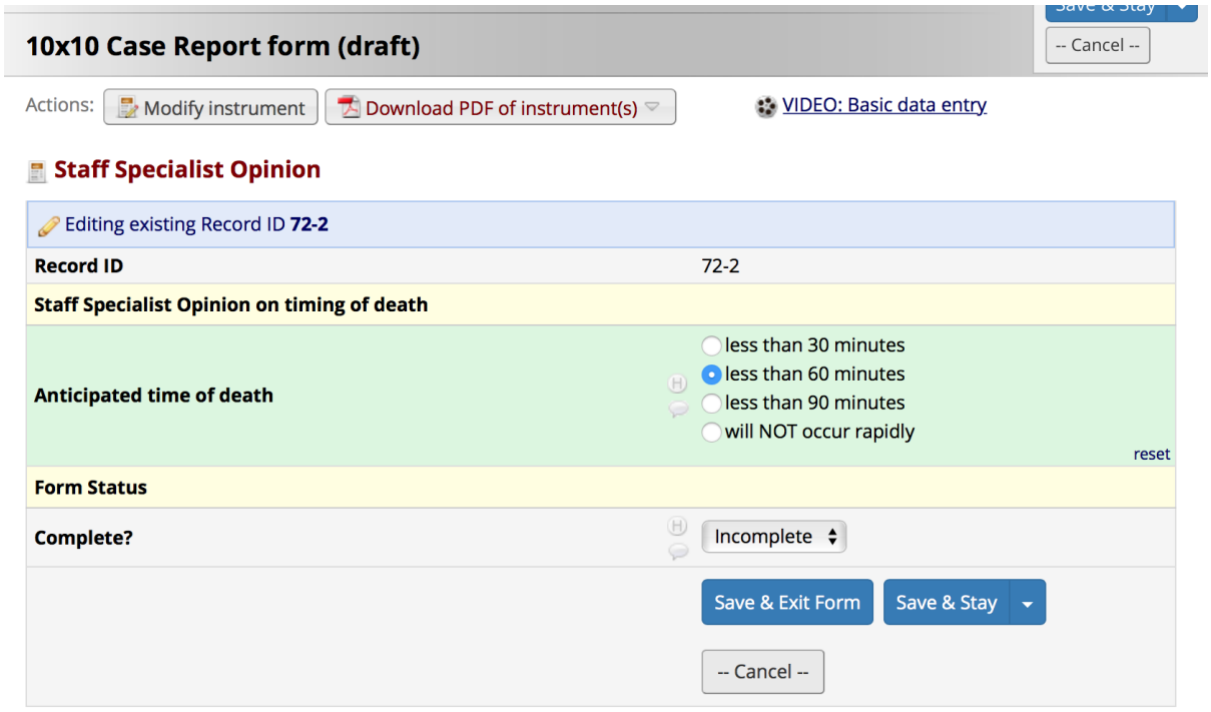
16. APPENDICES

16.1. RedCap Online Data Collection Form (sample pages)




Medications
(Please check units of infusions and align with those stated on this form)
Save & Exit For
Save & Stay
-- Cancel --
Yes
No
Vasopresssor
reset
Ionotrope
reset
Analgesia
reset
Sedation
reset
Vasopressor Name
Metaraminol
Noradrenaline
Vasopressin
Phenylephrine
Angiotensin agonist
Dopamine > 10 mcg/kg/min
Metaraminol Infusion rate (microg/min)
enter 0 if no infusion
Metaraminol Infusion dose (microg/kg/min)
expected range 0.05-1 microg/kg/min)
View equation
calculated field
Metaraminol cumulative (total) bolus dose in previous hour (microg)


10x10 Case Report form (draft)
-- Cancel --
Actions:
Modify instrument
Download PDF of instrument(s)
VIDEO: Basic data entry
Staff Specialist Opinion
Editing existing Record ID 72-2
Record ID
72-2
Staff Specialist Opinion on timing of death
Anticipated time of death
less than 30 minutes
less than 60 minutes
less than 90 minutes
will NOT occur rapidly
reset
Form Status
Complete?
Incomplete
Save & Exit Form
Save & Stay
-- Cancel --