Predicting time to asystole following withdrawal of life-sustaining treatment: a systematic review

## Craig Nicolson, Anique Burke-Robinson, Athanasios Tsanas, Laveena Munshi, Nazir Lone, Kathryn Puxty

# Abstract

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# Introduction

The prediction of asystole following the withdrawal of life-sustaining treatment (WLST) is important for informing families and to guide the identification of patients suitable for organ donation after circulatory death (DCD). These processes often occur in intensive care units (ICUs) (1) where patients are undergoing advanced life-sustaining treatments such as invasive ventilation or inotropic blood pressure support (2,3). The high levels of support provided by these treatments makes it complex to predict the course towards death following their withdrawal. The ability of physicians to make reliable predictions in this area is limited (4,5), and despite no formalisation is frequently the method used in clinical practice.

The DCD donation process is often complex, resource intensive and can be distressing for families (6). The occurrence of prolonged time to asystole frequently prevents successful donation as the organs are damaged due to stresses they undergo during this time. In the UK 45% of unsuccessful DCD donations are attributed to this reason (7).

Given the importance of this prediction a variety of predictive tools and models have been developed. Whilst some tools initially appear to perform well, these results are often not possible to externally validate. A lack of standardisation of the variables recorded and the specifics of the withdrawal process makes the transfer and shared use of developed tools challenging. These problems mean that widespread adoption or national deployment of such tools is uncommon. The aim of this systematic review is to evaluate the predictive performance of identified variables and developed models within the literature, with consideration of the common issues faced in tool development and validation.

# Methods

## Search strategy

We searched Ovid MEDLINE(R) and In-Process, In-Data-Review & Other Non-Indexed Citations (1946 to 2022 May 11) and Embase Classic+Embase (1947 to 2022 May 11). The searches combined Medical Subject Headings (MeSH), appropriate controlled vocabulary and keywords for time, death, and withdrawal as utilised in Munshi et al’s 2015 systematic review. The reference lists of all included articles and prior review articles were explored for further inclusions. Clinical experts were consulted to check the included articles for omissions identified through their expertise in the field. Conference abstracts, poster abstracts, letter responses and letters to editors were excluded.

## Study selection

Included articles were required to evaluate an adult population in an intensive care environment who underwent withdrawal of life sustaining treatment (WLST). Life sustaining treatment was defined as ventilation (invasive or non-invasive) or haemodynamic support. Measurement from WLST time to death or asystole was necessary for inclusion. Articles that did not evaluate potential predictive factors or models in relation to this measurement were excluded.

Two reviewers (CN, AB) independently reviewed all titles and abstracts identified from the literature searches. Of the articles not excluded in this process full text review was again undertaken by two reviewers. During both of these processes disputes were resolved by a third reviewer (KP).

## Data extraction and quality assessment

Data was extracted from the included articles using customised spreadsheets. Key population characteristics and measurement methods were recorded. The performance metrics of any evaluated predictive factors or models were recorded. Quality assessment was undertaken using the PROBAST (Prediction model Risk Of Bias ASsessment Tool) which was designed to assess the risk of bias (ROB) and applicability of diagnostic and prognostic prediction model studies.

## Data analysis

Given the lack of standardisation of the withdrawal process, heterogenous variable measurement and variation in time to asystole bracketing, data pooling or meta-analysis was not undertaken. Due to this the analysis consists of tabulation of study characteristics and performance metrics with summarisation of the literature as appropriate.

# Results

The initial Ovid MEDLINE and EMBASE via Ovid searches returned 1,145 and 1,969 results respectively to give a total of 2,418 articles to be screened following the removal of duplicates (Fig. 1). Screening of these produced 71 articles for full-text review with an additional paper from reference screening and from expert input. Full-text review produced 23 articles for inclusion in data extraction and analysis.

The populations (Table. 1) were relatively evenly split with 11 general populations (4,5,8–16) and 11 DCD eligible populations (17–27) with 1 article evaluating a DCD eligible population (28) that was a subset of a previously evaluated general population (8). The median age of the populations ranged between 41 and 66. Mixed ICU populations were the focus of 15 articles (4,5,8–10,12,14,16–20,22,24,27) with a total of 5,131 patients. Neurointensive care populations were the focus of 4 articles (11,15,23,25) with a total of 1,181 patients The remaining 3 articles (13,21,26) did not specify the type of ICU that the patients originated from totalling 757 patients.

The majority of articles included death within 60 minutes in their evaluation of variables and/or models with the exception 5 (10,12,16,24,26) that did not evaluate this outcome. The percentage of patients who died within 60 minutes ranged from 44-76% across these articles. Eight articles (4,13,15,17,18,23,24,27) included death within 120 minutes which ranged from 54-91% of included patients.

Mechanical ventilation was stopped at the point of WLST in all articles with the cessation of vasoactive agents in the majority. The specific process of withdrawal was not typically detailed with only 5 articles (17,19–21,27) specifying that withdrawal of all active treatments was simultaneous.

## Predictive Variables

Seven articles (10,12–14,16,20,24) did not derive or validate any predictive models and instead focused on the identification and/or evaluation of predictive variables. The variables found to be associated with death within 60 minutes using multivariable logistic regression are detailed in Table 2.

Several variables were identified in multiple analyses. Five analyses identified a measure of oxygenation (i.e oxygenation index, PaO2, or FiO2) with effect estimates ranging from 1.01 to 3.36. Four analyses identified the presence of corneal reflexes, cough reflex and motor response with effect estimates ranging from 0.32 to 3.76, 0.45 to 4.47 and 0.41 to 2.99 respectively. Blood pressure measurements and the use of vasopressors were both identified in three separate analysis with effect estimates ranging from 0.80 to 0.99 and 1.67 to 3.02 and respectively. Two analyses identified the use of comfort medications following WLST with effect estimates ranging of 0.35 and 1.15. The final variable identified in multiple analysis was PEEP (positive end expiratory pressure) with effect estimates of 1.07 and 1.17.

## Predictive Modelling

The derivation or modification of predictive models occurred in 7 articles (4,8,13,15,17,21,28), the external validation of an existing model was undertaken in 3 articles (19,23,25), and a mixture of both was undertaken in a further 5 articles (5,9,18,22,27) (Table. 3). All articles included the evaluation of models for prediction of death within 60 minutes whilst some included evaluation of death within 120 minutes or other ranges. In total 15 unique models were reported with several articles reporting results when refitting these models.

Two of the models evaluated were developed using clinical experience and expert consensus without the reported use of statistical techniques (9,18). Of the remaining models two used classification and regression trees (CART) (9,28), two models used cox regression analysis (15,20) and seven models used other forms of multivariable regression analysis (5,8,13,17,21,22,27). The final 2 models used random survival forests (RSF) (4), and a light gradient boosting machine (27) respectively.

At the point of derivation or modification validation procedures were varied, with 5 articles evaluating model performance against the same cohort using for model fitting (5,9,17,18,27), with only 1 of these using cross validation to attempt to mitigate the impact of overfitting (27). Four models were validated at the point of derivation by splitting the cohort into training and testing sets (4,8,22,28), with a further four validated using an external cohort. One model was validated using a prospective cohort and one was validated using both an external cohort and a prospective cohort.

Of the performance evaluations at model derivation or modification reported AUCs for the 60 minute models ranged from 0.73-0.99, sensitivities from 0.39-0.87, specificities from 0.13-0.96, PPVs from 0.34-0.93 and NPVs from 0.27-0.84.

Sixteen instances of secondary validation (validation by another group) were observed across 6 articles (5,19,22,23,25,27) with 3 of these articles solely attempting to validate previously derived models without any model derivation or modification.

Of the secondary validations the reported AUCs for 60 minute models ranged from 0.45-0.88, sensitivities from 0.42-0.88, specificities from 0.46-0.84, PPVs from 0.36-0.76 and NPVs from 0.62-0.92.

The University of Wisconsin DCD tool (UWDCD) (18) is a scoring system developed using clinical experience that requires a 10 minute period of ventilator disconnection during which any spontaneous respirations are evaluated for rate, tidal volume, negative inspiratory force and saturations. The tool thresholds these measurements alongside the number of agents used for blood pressure support, patient age and airway type. Initial validation using 43 patients within the hospital area in which the tool was developed showed a sensitivity of 0.87 and specificity of 0.80 (18). During this validation the authors also explored the inclusion of BMI yielding a sensitivity of 0.84 and specificity of 0.85. Two articles externally validated the tool that included BMI in larger populations where the performance was not replicated with sensitivities of 0.42 and 0.45 and specificities of 0.61 and 0.49 (5,23).

The United Network for Organ Sharing tool (UNOS) (9) was developed using committee consensus and was evaluated in 3 articles. It is a criteria based scoring tool with higher scores corresponding to a patient meeting more criteria (Table 3) and accordingly a higher chance of death within 60 minutes. As with the UWDCD to original criteria require a period of ventilator disconnection. Two evaluations of the full criteria produced an AUC of 0.53 (23) and a PPV of 0.63 (9). Coleman et al.’s evaluation used a modified UNOS tool where the period of ventilator disconnection was omitted and replaced with definitions of ventilator dependence and oxygen disruption and this was found to give a sensitivity of 0.61 and specificity of 0.84.

Devita et al. (9) developed a predictive tool using CART model analysis which took GCS ≥ 4, SaO2/FiO2 ≥ 2.3 and PIP ≥ 35 as inputs. The performance was evaluated directly on the derivation cohort giving a sensitivity of 0.75 and specificity of 0.73.

The Hunter New England Area Composite score (5) was developed using logistic regression and achieved sensitivity of 0.56 and specificity of 0.13 when using the definitions of ventilatory dependence and oxygen disruption. The inclusion of a systolic blood pressure threshold produced performance of 0.39 and 0.96 respectively. These evaluations again directly used the derivation cohort and no external validations have been published.

Davila et al. (21) used multivariable regression analysis to develop a tool that took the binarized variables of inotrope use, age of 40 or under and gag reflex presence. The original authors validated the tool using a prospective cohort to give an AUC of 0.83. External validation across 3 cohorts yielded AUCs of 0.80, 0.70 and 0.80 (19,27).

The DCD-N tool is based on corneal reflex, cough reflex, motor response and oxygenation index as identified by Yee et al. (11) using logistic regression. This group later validated the model through fitting with a prospective cohort (13) finding a sensitivity of 0.81 and 0.73. Three articles externally validated this model giving AUCs of 0.75 (22), 0.69 (23) and 0.77 (25). In addition to externally validating the model de Groot et al. also propose a modified model using a continuous oxygen index which was externally validated across 4 cohorts giving AUCs of 0.75, 0.86, 0.74, 0.86 (19,25,27).

Wind et al. (17) used logistic regression to develop a model that used the binarized presence of: controlled mode ventilation, norephinephrine use, cardiovascular co-morbidity, brainstem reflexes and neurologic deficit. This achieved an AUC of 0.73 within the derivation cohort which fell to 0.62 in a subsequent external validation (19).

Brieva et al. developed models in a general population (8) and later in a DCD subset of this population (28). All of these models used ranges of PEEP, spontaneous respiratory rate, GCS and systolic blood pressure, with the inclusion of ICU specialist opinion used to define a second model in both populations. Using internal validation cohorts the models achieved sensitivities of 0.82 and 0.78 and specificities of 0.59 and 0.89 in the general and DCD populations respectively. The inclusion of ICU specialist opinion in these models improved performance to sensitives of 0.84 and 0.83, and specificities of 0.72 and 0.94 respectively.

The C-DCD model is a nomogram that was developed using cox regression analysis to identify 10 variables for inclusion (Table 3). The authors used 2 validation cohorts (external and prospective) to evaluate the model and report AUCs of 0.94 and 0.99. A subsequent external validation demonstrated slightly worse performance with an AUC of 0.88.

The first model to incorporate time series rather than instantaneous data into a prediction model was developed by Scales et al. (4). Here random survival forests used physician predictions alongside a series of variability features of blood pressure and heart rate time series. An internal validation cohort demonstrated an AUC of 0.79 using this model.

Finally, alongside the validation of 2 previous models, Kotsopoulos et al. evaluated 2 new models, one using LASSO regression analysis and another using a light gradient boosting machine (LightGBM) (27). The LASSO regression analysis model achieved an AUC of 0.80 in an external validation cohort and the LightGBM model achieved an AUC of 0.79 in 10-fold cross validation.

# Discussion

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# Conclusion

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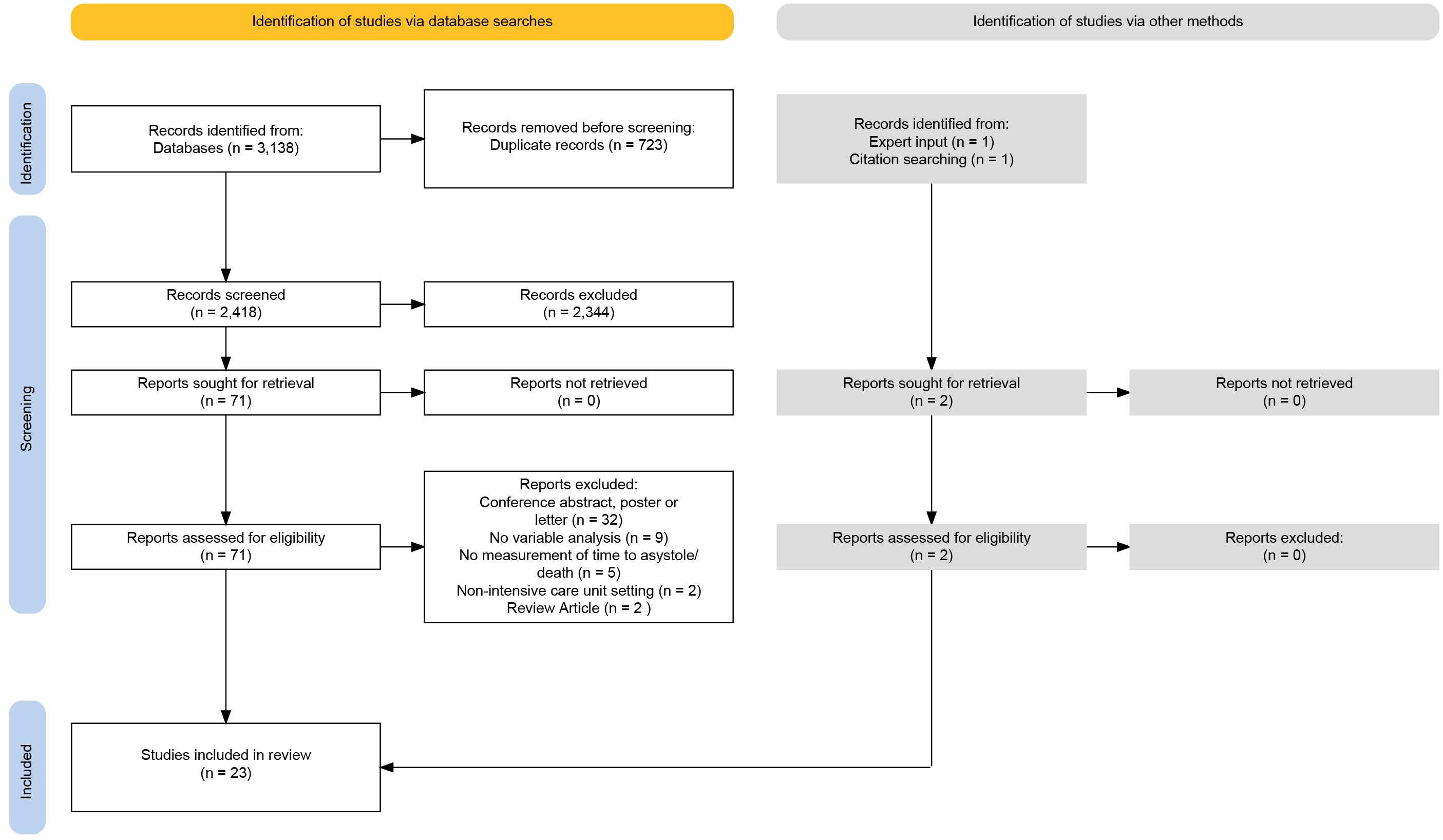


Figure : PRISMA Diagram



Table : Cohort characteristics, withdrawal parameters and measured outcomes



Table : Risk factors associated with time to death <60 minutes in multivariable analyses







Table : Prediction model variables, methods and performance. \* Measured after a 10 minute period of ventilator disconnection. \*\*First published validation of a tool without initial published derivation.\*\*\*Validation cohort was from the author's previous study that was used to identify model variables but not for fitting. \*\*\*\*Based on the continious oxygen index as modified by de Groot et al. then refitted by Rabinstein et al. \*\*\*\*\*Validation of the variable combination identified by Yee et Al. before the authors evaluated them in the DCD-N model.

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# Appendix

## Appendix 1 – Embase Classic+Embase Search Terms

1. Treatment Withdrawal/
2. ((withdraw\* or withhold\* or limitation\*) adj3 (life support or life sustaining or mechanical\* ventilat\*)).tw.
3. ((withdraw\* or withhold\* or limitation\*) adj2 (treatment\* or therap\*)).tw.
4. treatment cessation\*.tw.
5. or/1-4
6. exp Death/
7. (death or dead or die$1).tw.
8. exp time/
9. exp survival time/
10. time.tw.
11. (6 or 7) and (8 or 9 or 10)
12. (predict\* adj2 death\*).tw.
13. brain death\*.tw.
14. brain stem death\*.tw.
15. cardiac death\*.tw.
16. cardiocirculatory death\*.tw.
17. cardio circulatory death\*.tw.
18. dcd$1.tw.
19. circulatory death\*.tw.
20. clinical death\*.tw.
21. diagnosis of death\*.tw.
22. determination of death\*.tw.
23. or/11-22
24. 5 and 23

## Appendix 2 – Ovid MEDLINE(R) and In-Process, In-Data-Review & Other Non-Indexed Citations Search Terms

1. exp Withholding Treatment/
2. exp life support care/
3. ((withdraw\* or withhold\* or limitation\*) adj3 (life support or life sustaining or mechanical\* ventilat\*)).tw.
4. ((withdraw\* or withhold\* or limitation\*) adj2 (treatment\* or therap\*)).tw.
5. treatment cessation\*.tw.
6. or/1-5
7. exp Death/
8. (death or dead or die$1).tw.
9. exp time/
10. time.tw.
11. (7 or 8) and (9 or 10)
12. (predict\* adj2 death\*).tw.
13. brain death\*.tw.
14. brain stem death\*.tw.
15. cardiac death\*.tw.
16. cardiocirculatory death\*.tw.
17. cardio circulatory death\*.tw.
18. dcd$1.tw.
19. circulatory death\*.tw.
20. clinical death\*.tw.
21. diagnosis of death\*.tw.
22. determination of death\*.tw.
23. or/11-22
24. 6 and 23