Validation of a novel scoring system to predict inpatient mortality in exacerbations of Chronic Obstructive Pulmonary Disease requiring assisted ventilation with supplementary longitudinal assessment of quality of life and other patient-centred outcomes over one year.

Sponsor:

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Scientific Abstract:

Background: Exacerbations of COPD account for 12% of UK hospital admissions and are frequently complicated by respiratory acidaemia, which has a high in-hospital mortality rate. In acidaemic exacerbations, mortality is reduced 2-3 fold by non-invasive ventilation (NIV). NIV is now part of standard care and delivered on admission units or respiratory wards, including dedicated areas, in most cases. Decisions regarding suitability for NIV are often made by non-specialist or junior clinicians. There is significant underutilisation of NIV perhaps reflecting prognostic nihilism, including among specialists. In survivors, acidaemic respiratory failure frequently recurs and post-discharge mortality is high. Presently, little is understood regarding health-related quality of life (QoL) post discharge or patients' wishes for repeated NIV were it to be required.

Aims: We are currently developing a simple bedside prognostic tool to predict inpatient mortality in acidaemic exacerbations of COPD and augment clinical decision making. In the proposed study we aim: 1) To validate the derived tool in 6 centres in the UK. 2) Among those surviving to discharge to: a) identify predictors of 6 month mortality; b) assess 12-month outcomes including: survival, QoL, functional status and readmissions and compare results in pre-specified subgroups; c) explore patient views on their QoL and willingness to undergo NIV again in the future.

Methods: At least 425 patients will be prospectively recruited. We will collect descriptive indices, clinical data to enable calculation of: the components of the derived tool; APACHE II; CAPS; and Risk of failure chart, and other indices independently related to mortality within the derivation study. Performance of the derived tool will be assessed by examining discrimination, calibration and generalisability for inhospital mortality, and discrimination will be compared between tools. Predictors of 6 month mortality will be identified. Outcomes in pre-defined subgroups potentially conferring high mortality will be described. In consenting patients who survive to discharge, QoL, functional capacity, exacerbation rate and willingness to undergo NIV again will be recorded longitudinally.

Benefits: We anticipate this study will augment and improve patient-centred decision making surrounding NIV initiation and enable more informed advanced care planning in patients surviving acidaemic respiratory failure. Accurate prediction of outcome can challenge pervasive nihilism. Furthermore, identifying patients with very poor prognosis may enable improved end-of-life care, including specialist palliative care, in appropriate patients.

Plain English Summary:

Chronic obstructive pulmonary disease (COPD) is a common lung disease and accounts for a large number of hospital admission each year. COPD is frequently complicated by episodes of acute worsening of respiratory symptoms, termed 'exacerbations'. Severe exacerbations of COPD may lead to respiratory failure. Non-invasive ventilation (NIV) is a method of supporting the patients' normal breathing efforts, using a mask fitted to their face connected to a ventilator, and can be life-saving during exacerbations of COPD complicated by respiratory failure. Compared to invasive ventilation, which involves placing a tube in the patients main airway, sedation is avoided, complications such as infection are less common, outcomes better and a much larger proportion of patients are considered eligible. The earlier NIV is started, the better the outcomes for patients. Historically NIV was provided in intensive care units, but it has been shown to be safe and effective when delivered in non-intensive care settings. Therefore, over recent years there has been an appropriate expansion in NIV use and the decision to initiate NIV is now undertaken by a variety of clinicians, including non-specialists. Despite widespread availability there is significant underuse of NIV. Clinicians initiating NIV need to be able to quickly identify which patients would benefit from NIV and which patients may require alternative therapies. This complex decision requires an assessment of an individual's chances of survival, should NIV be provided. Of concern, even specialist clinicians are unduly pessimistic about outcomes following NIV, which may lead to patients being inappropriately denied treatment.

A simple, reliable tool to objectively identify patients likely to benefit and augment clinical decision making has tremendous potential to further increase appropriate use of NIV. We are currently deriving a predictive tool, using indices that are readily available and designed to be easy to apply at the bedside, to predict inpatient mortality in exacerbations of COPD requiring assisted ventilation. In a pilot study, we have identified novel predictors of in-patient death and are confident that we can develop a tool with strong performance. Before a predictive tool can be used in clinical practice, it is vital to ensure it is generalisable to other hospitals and other geographical locations. Therefore, our application is to fund a prospective multicenter study to validate this tool. The majority of funding represents staff costs at participating sites with additional allocation for statistical support, logistics and distribution of completed manuscripts. The benefits of this work are numerous; primarily we anticipate increasing the use of lifesaving treatment (NIV) by improving clinical decision making (principally challenging nihilism). Identifying predictors of 6 month mortality is valuable for discharge planning and can improve patient-centred decision making regarding future care, including provision of palliative care. In addition to validating the predictive tool we intend to follow up consenting patients with particular focus upon quality of life after assisted ventilation. Patient and public opinion has been sought with strong support voiced for the project. Our research team has a history of delivering high quality, high impact research on time and on budget. We believe the proposed study has potential to yield practice changing results.

Background:

In the UK, approximately three million adults have COPD.[1] Globally it is estimated to be 210 million, 65 million of whom suffer moderate to severe disease. By 2030, COPD is projected to be the 4th leading cause of death worldwide,[2] between 1970 and 2002 the death rate from COPD in the USA doubled and is continuing to rise.[3 4] Acute exacerbations of COPD (AECOPD) account for ~12% of all hospital admissions in the UK,[1] and are associated with substantial morbidity and mortality. In severe exacerbations complicated by acute respiratory failure (respiratory acidaemia) non-invasive ventilation (NIV) reduces the

risk of death 2–3 fold in both ward based [5] and intensive care settings,[6] including in comparison to invasive ventilation.[6] Early initiation of NIV is an independent predictor of survival,[7 8] highlighting the importance of rapid and accurate identification of patients who may benefit.

Despite proven efficacy, there is underutilisation of NIV: the 2008 UK COPD audit showed that 26% of patients had respiratory acidaemia during their admission, but only 12% of patients received ventilatory support.[9] This is in spite of near universal availability (UK ward based NIV availability was 97% in 2008 99.8% in 2015). Respiratory acidaemia will correct with medical therapy in approximately 20% of cases.[10] Therefore, even if trials of medical therapy, including controlled oxygen, were routinely performed, there is substantial underutilisation of NIV. The most recent National UK COPD Audit report (Feb 2015) showed little improvement in the proportion of patients receiving NIV (12%).[11] The reason for underutilisation of NIV is multifactorial but, in-part, reflects prognostic nihilism which is unfortunately widespread in this setting.[12] This audit also showed standardisation of care between and within institutes is lacking: mortality varies both geographically and by day of week admitted.[11] This is not unique to the UK: US guidelines recommend an initial trial of NIV in exacerbations of COPD complicated by respiratory acidaemia but a review of national practice from 1998-2008 showed large regional variations in both age and practice suggesting there is a significant non-conformity of approach.[13] Similarly in Scandinavia NIV was used in only 14% of the admissions, with large variation between centres.[14] Increasing use of NIV has been recognised by NHS England ("Reducing Premature Mortality")[15] and the Department of Health ("An Outcomes Strategy for COPD and Asthma")[16] as a key priority.

An estimation of the likelihood of survival is fundamental to the decision to initiate NIV. Clinicians' prognostic estimates have been shown to be inaccurate with widespread prognostic pessimism. The multicentre COPD and Asthma Outcomes Study (CAOS) compared clinicians' estimated six month survival with actual outcomes. In the lowest quintile, estimated survival was 10% compared to actual survival of 40%. Moreover, in the 10% of patients which clinicians estimated to have the lowest survival (3%), actual survival was 36%.[12]

Existing prognostic tools for use in this population offer only modest prognostic performance. Implementation has been further limited because they are: complex and difficult to apply in routine clinical practice; developed in a highly selected population managed on intensive care (in the UK, NIV for AECOPD is usually delivered on medical wards); or predict failure of ventilation not mortality. In the largest such study by Confalonieri et al.[17] a 'risk of failure chart' was developed but its performance was modest (c statistic = 0.71) and the tool is complex to calculate. The development of a simple, accurate prognostic tool would augment clinical decision making, improving use of NIV and potentially reducing mortality in this common and frequently fatal condition. From pilot data (n=199),[8] we are confident we can develop a suitable tool. Of importance, we have identified several strong independent prognostic variables that were not included as potential predictors during the development of existing tools.

While the predominant anticipated gain of robust prognostication is increasing NIV usage, recognising patients unlikely to survive who have little chance of benefit from NIV is equally important. Mortality is higher in national audits than randomised controlled trials (34% v. 7-13.7%).[5 17-21] In part, this reflects selection criteria applied within clinical trials, however such large differences suggest that NIV is being used when there is little chance of success. NIV can be difficult to tolerate and may cause distress when alternative palliation would be more appropriate. Compared to patients with advanced malignancy, patients with severe COPD report poorer health-related quality of life (QoL) and higher levels of anxiety and depression.[22] Despite this, palliative care is underutilised in patients with COPD, in part reflecting

difficulty in predicting outcomes. Early identification of patients unlikely to survive will enable timely symptom control and better end of life care.

The national COPD audit [9] identified that, contrary to national guidelines,[23] consultants are infrequently involved in the decision to initiate NIV. Similarly 'ceiling of care' decisions are made in less than half of cases.[11] Patients often deteriorate out of hours with complex decisions taken by the on-call clinical team, in patients who may be to unwell to communicate their wishes and expectations. Consequently, there is a drive towards proactive treatment escalation planning, whereby potential treatment options, if clinical deterioration were to occur, are discussed with a stable patient and a patient-centred escalation plan can be made by a senior clinician. Such discussions require an accurate estimation of survival. A prognostic tool, using data available at the time of hospital admission, to predict a patient's chance of survival were they to subsequently deteriorate, would enable accurate evidence-based escalation planning and facilitate more patient-centred care.

Short-term mortality is not the only important outcome for patients and therefore should not be the sole outcome in prognostic research; we will capture mortality data to one year and beyond.

Outcomes in several pre-defined sub-groups potentially conferring high mortality will be examined, including patients: 1) with late failure of NIV; 2) with persistent hypercapnia [24] at discharge; 3) requiring long term oxygen therapy (LTOT); 4) those receiving long-term NIV and 5) eosinopenia at discharge. Late failure is defined as recurrent respiratory acidaemia at least 48 hours after NIV initiation, whilst still receiving NIV. The single previous study of late failure of NIV showed very poor outcome, particularly if NIV was continued in this setting (survival to discharge: NIV continued = 8%; invasive ventilation = 47%).[25] This result has informed national guidance which recommends either invasive ventilation or palliation if late failure occurs. Data from the National COPD audits suggest few patients (≈1%) with respiratory acidaemia are invasively ventilated and our practice is to initially offer high intensity NIV to those who develop late failure. Pilot data from our institution has shown good outcomes in our cohort managed with high intensity NIV: 64% survived to discharge.[26] We will examine this further in the planned study and if the conclusions from the pilot data are confirmed, national guidance should be updated.

In addition to an estimation of the likelihood of survival and the patients' wishes, it is recommended that decisions regarding the use of NIV in an individual patient include an assessment of whether the individual patient has "potential for recovery to quality of life acceptable to the patient"[23]. There is scarce published data describing the expected QoL change following NIV and therefore an improved understanding of the expected changes in QoL and functional status could help inform patient-centred decision making regarding the use of NIV. We believe this additional prognostic information would be of significant benefit patients and clinicians.

The focus of this study has been recognised by NHS England and the Department of Health as a key priority and successful completion of this study can: provide important data in an under-researched area; influence national guidelines; and significantly improve patient care.

Public and Patient Involvement:

Patients and public opinion has been sought throughout the development of this project and has influenced many aspects, including the aims, design, and planned implementation and dissemination. The feedback on the study was overwhelmingly positive. The local Research Design Service Patient User Group

representing a broad spectrum of disease including COPD was consulted. Additionally, we established a local COPD focus group including patients and carers with experience of NIV who offer a disease specific viewpoint. Lay person, general medical and disease-specific opinions were obtained and informed our decisions. Numerous improvements have been made as a direct result of patient and public consultation. For example the shorter COPD Assessment Test (CAT)[27] was substituted for the St Georges Respiratory Questionnaire which we had originally planned to use.[28]

The project aims were universally supported giving the proposals a strong mandate. There was concern regarding the underutilisation of NIV nationally and particular enthusiasm from patients for increasing NIV uptake. Carers stated that improved prognostication would reduce anxiety generated by recurrent admissions each with uncertain outcome.

This feedback has cemented our pre-existent priority that this project's main focus is to optimise NIV uptake and challenge prognostic nihilism, thereby improving patient outcomes. However, in addition, the focus groups, including patients with personal experience of NIV, confirmed that NIV can be intrusive and they would only agree to treatment if it were likely to confer benefit. This supports the need for simple, robust prognostic tools to identify those patients unlikely to survive, as well as those likely to benefit.

Aims:

The principle aim of the proposed study is to prospectively validate, in multiple UK hospitals, a prognostic tool aiming to accurately predict survival, and help inform clinical decisions, in patients with acute exacerbations of COPD requiring NIV.

The derivation of this tool is on-going, is progressing on target and is not the subject of this application. The derivation study will develop prognostic tools to predict in-hospital survival using: a) indices available on admission; b) all indices up to the time of clinical deterioration. The tool limited to indices available on admission offers the advantage of informing discussions between the patient, their family/carers and the senior clinician regarding 'escalation planning' (i.e. whether it would be appropriate to initiate NIV should the patient have, or subsequently develop, respiratory acidaemia). Whilst this offers clear advantages, including all variables up to the point of clinical deterioration may result in a more accurate prognostic tool. We will be compare the performance of both novel tools to identify the most clinically useful predictive instrument. Performance will also be compared to existing tools and this analysis will be repeated in the proposed validation study

Principle Aims:

1. Prediction of in-hospital mortality

    - The derived tool(s) will be validated prospectively, both temporally and geographically, in at least 6 diverse sites in the UK, chosen to ensure wide variation in socio-economic factors, COPD prevalence, rurality and structures of care.

2. To identify predictors of death within six months.

- Patients who survive the initial episode requiring NIV continue to have a high mortality and readmission risk following discharge. Accurate prediction of short and medium term survival, in those patients surviving the initial admission, may further inform decisions about escalation to assisted ventilation acutely and during subsequent episodes of acute deterioration and help patients make more informed decisions regarding other aspects of care planning. This may improve access to palliative care services, currently underutilised in this condition.

3. To assess 12-month survival and readmissions both in the overall population and in patients with, and without, other key characteristics, including:

- Late failure of NIV (recurrent respiratory acidaemia, despite on-going ventilatory support).

- Persistent hypercapnia.

- Long-term oxygen therapy.

- Long-term ventilation on discharge.

- Eosinopenia at discharge.

4. In consenting patients who survive to discharge, we will assess:

a) Longitudinal QoL (CAT[27] and EQ-5D 5L[29]) and functional status (NEADL [30]), and identify predictors of poor baseline QoL with a subsequent clinically significant deterioration (poor recovery).

b) Hospital Anxiety and Depression scale (HADS [31]), and relation to readmission and mortality risk.

c) Patients' views regarding their recent experience of NIV and their willingness to undergo similar treatment again during subsequent severe exacerbations.

Pilot[8]/Derivation Study

Methodology: Observational cohort of consecutive patients hospitalised with AECOPD. Of 920 consecutive patients hospitalised with AECOPD, 199 received assisted ventilation (NIV only = 191, Invasive ventilation only = 4, NIV progressing to invasive ventilation = 4) for acidaemic respiratory failure (pH <7.35, paCO2¬ >6 kPa). Univariate associations with in-hospital mortality were identified and variables associated with mortality (p <0.10) were entered in to logistic regression analysis. Variables were categorised or dichotomised prior to regression analysis. The strongest independent predictors were used to formulate a prognostic tool. Individual prognostic variables were assigned a weighting relative to their regression coefficient (β). Discriminative strength of the prognostic tool was quantified using AUROC.

Of importance, we identified two novel independent predictors of outcome, not considered in the development of previous instruments; a) stable state breathlessness as assessed by the eMRCD, and b) timing of acidaemia (time from admission to acidaemia > 4hrs). Combined with severity of acidaemia (pH< 7.25), these indices offer strong discrimination, AUROC = 0.803; CI 0.73-0.87, and outperform alternative and more complex tools within their derivation cohorts (Confalonieri = 0.71, CAPS = 0.72, APACHE = 0.65).

A prognostic tool incorporating the strongest six predictors of mortality among indices gathered up to the time of clinical deterioration (eMRCD, time from admission to acidaemia >4 hours, cough effectiveness, serum albumin <35 g/dL, respiratory rate >30/min, pH <7.25) further improved prediction of in-hospital mortality: AUROC = 0.862; CI 0.80 – 0.92. A prognostic tool limited to only indices available at the time of

hospital admission (eMRCD, cerebrovascular disease, age >80 years, recent >5% weight loss, radiographic consolidation, blood neutrophil count >12.5 x10^9/L) offered similarly strong discrimination, AUROC = 0.848, 0.79 – 0.91, and offers the advantage of facilitating discussions between the senior attending clinician, the patient and their family regarding escalation decisions.

The proposed tools will be further refined within the planned derivation cohort (n=425), prior to undergoing formal validation. However, this study demonstrates the feasibility of our planned research proposal and we anticipate that the larger derivation cohort will allow the development of a robust, accurate prognostic tool, designed to be easily applied at the bedside to inform discussions between clinicians, patients and their families and lead to more appropriate use of NIV, improving outcomes for patients.

Experimental Design and Methods:

Validation Study

425 patients will be enrolled, split between internal and at least five external sites. The research proposal has been presented to the UK NIV Research Network, gaining strong endorsement. Several sites, including St Thomas' London, St James University Hospital Leeds and Nottingham University Hospitals are keen to participate. Sites outside the network will also be considered, provided they can offer appropriate resources and experience. It is essential that participating sites offer NIV liberally; exclusion of a substantial proportion of patients with limited performance status or other characteristics would bias the study. In our unit, of patients meeting criteria for NIV who are unable to leave their house unassisted and require help with washing and dressing (i.e. poorest performance status), 86% receive NIV. Consequently we are ideally placed to derive and validate the prognostic tool. The site selection process will ensure a reasonable balance in demographic, socio-economic, ethnic and geographical (region and rural/ urban divide) diversity. At each site, consecutive, unique patients meeting the selection criteria will be identified by prospective screening of the admission unit and areas where NIV is provided (invasively ventilated patients will be included, but separately identified). Descriptive indices collected will be similar to the derivation study, but predictive indices will be restricted to the composites of APACHE II,[32] CAPS,[33] NIV Risk Chart[17] and indices independently related to mortality within the derivation study. Ventilator settings at initiation and peak support, and the duration of ventilation, will be recorded. In patients experiencing late failure of NIV, ventilation settings prior to late failure and following intensification of NIV, and details of the cause of late failure, will also be captured. Similar data will be captured in those experiencing relapse (recurrent respiratory acidaemia post weaning). Pre-discharge arterial blood gas will be performed. Survival data will be collected to 12 months post discharge.

It is likely that during the prospective validation some patients will receive NIV who, in the opinion of the attending clinician and experienced site PI, have a diagnosis of COPD but no spirometry is available for formal inclusion. We believe that once the tool is adopted in clinical practice, it is likely to be applied to such patients. For this reason in these circumstances we propose collecting an extremely reduced dataset (simply demographics, the components of the score and survival data). These patients will not count towards the minimum number of patients to achieve power.

Longditudinal Study

This component of the trial will be amongst survivors and will require individual patient consent. A better understanding of outcomes, should a patient survive to discharge, will help inform discussions about future care planning. Sites will either be an 'a' site or a 'b' site:

'a' sites will collect survival and readmission data in all and in addition (in consenting patients) collect attitudes towards future NIV at discharge and at 3 months: 1) "considering your recent experience on ventilation and how you feel at present and about the future, are you glad that you received ventilation?"; 2) "based on your recent experience, if faced with a similar severe exacerbation in the future would you choose to receive ventilation again?" and; 3) "are you satisfied with your current overall QoL?". Patients will be reminded of the episode of ventilation referred to, and that on average, NIV reduces the risk of death in hospital by approximately two fold.

'b' sites will undertake more in depth longitudinal assessments. In addition to 'a' requirements 'b' will capture the following: QoL will be assessed using the COPD Assessment Test (CAT) [27] and EQ-5D 5L.[29] Functional status will be assessed using the Nottingham Extended Activities of Daily Living scale (NEADL)[30] and eMRCD.[34] Anxiety and depression will be assessed using the Hospital Anxiety and Depression Scale (HADS).[31] Scheduled assessments will be conducted by a researcher at baseline, three, six and twelve months, and will also include spirometry, oxygen saturation and BMI. Between scheduled assessments, patients will be asked to record monthly CAT, EQ-5D-5L, NEADL, eMRCD, HADS, exacerbation and health resource utilisation data (patient completed assessments). Health resource utilisation will also be collected electronically.

Inclusion and Exclusion Criteria:

To ensure the tools derived are generalisable, all patients consecutively admitted with AECOPD requiring assisted ventilation will be screened.

Inclusion Criteria:

1. Age 35 years or older.

2. Smoking history greater than or equal to 10 pack years.

3. Obstructive spirometry (FEV1/FVC < 0.7).

4. AECOPD primary diagnosis.

5. Respiratory acidosis treated with NIV or IPPV (arterial blood gas pH <7.35, pCO2 > 6.5).

Exclusion Criteria:

1. Previous inclusion in the study.

2. Other illness likely to limit survival to less than 1 year.

Outcomes:

Primary Outcome:

Prediction of in-hospital mortality within the validation cohort assessed by the area under the receiver operating characteristic (AUROC) curve for tools developed using:

a) Indices available on admission.

b) All indices up to and including the time of deterioration.

Secondary Outcomes:

In the admitted population:

1) Comparison of the AUROC curves for both novel tools.
2) Comparison of the AUROC curves for both novel tools to CAPS, APACHE II and Confalonieri risk chart.

Among patients surviving to discharge:

3) Mortality to 1 year.
4) Readmission rates at 30, 90 and 365 days.
5) Comparison of outcomes in patients with, and without pre-defined characteristics:
    a. Late failure of NIV (recurrent respiratory acidaemia, despite on-going ventilatory support; in-patient mortality will also be captured).
    b. Persistent hypercapnia.
    c. Long-term oxygen therapy.
    d. Long-term ventilation on discharge.
    e. Eosinopenia (<0.05 10^9/L) at discharge
6) Longitudinal changes in patient reported outcomes (CAT, eQ-5D-5L, NEADL, HADS) post discharge, quantified by calculating: mean change (relative to the minimum clinically important difference (MCID)); duration maintained above baseline; and time taken to reach peak.
7) Predictors of a) 6 month mortality and b) poor baseline QoL with a subsequent clinically significant deterioration (poor recovery).
8) Relation between clinically significant anxiety and depression on discharge and: survival, QoL, functional status and readmission rate.
9) Examination of patient willingness to undergo ventilation again in the future.

Long-term treatments likely to influence outcome, and eosinophil counts by varying thresholds on discharge, will be captured and their association with readmission and mortality assessed.

Statistical Analysis:

Power:

In order estimate the sensitivity of the tool (and assuming a standard error of 5%) 85 deaths should be studied in the cohort. Assuming a mortality rate of 20% at least 425 patients are required in both the derivation and validation cohorts.

Missing Data:

For both derivation and validation cohorts, missing variables will be imputed by expectation maximisation algorithm, to minimise bias. All subsequent analysis will be performed on complete dataset. Comparison to original dataset will be made to ensure no statistically significant discrepancy.

Population Description

Parametric variables will be identified by visual inspection of the histogram. To characterise the patient sample, proportions will be used for categorical variables, means with standard deviations (SD) for parametric variables, or medians with inter-quartile ranges (IQR) for non-parametric variables. To compare characteristics and outcomes between population groups, Fishers' Exact Test will be used to compare categorical variables, Student's T-test to compare parametric data, and Mann-Whitney U to compare non-parametric variables. To examine for trends across multiple sites, ANOVA will be used for parametric data and Kruskal-Wallis for non-parametric variables.

Outcome analysis:

Derivation study

The statistical methodology during derivation of the tool is described for completeness. Variables related to mortality ($p < 0.1$) on univariate analysis will be identified using student's t-test, Mann Whitney U or Fisher's Exact test for parametric, non-parametric and categorical data respectively. Multicollinearity will be assessed and handled according to the recommendations by Field.[35] Continuous variables will be dichotomised or categorised, with groups identified by the following hierarchy: a) inspection of the receiver operating characteristic curve; b) a clinically relevant threshold; c) median split. Variables with < 10% of the population in one category will be excluded. Eligible variables will then be entered into backward stepwise logistic regression, with in-hospital mortality as the dependant variable. To assess whether the final model is a good representation of the observed population, outliers will be identified by screening studentised residuals and further assessed by leverage values. Calibration will be assessed by Hosmer-Lemeshow goodness-of-fit test. To ensure that the final model can be easily applied at the bedside, the final number of variables will be reduced to the minimum required to maintain good, or very good, prediction of in-hospital mortality. Weightings of the individual prognostic indices will be assigned according to the regression coefficient (B). Performance will be assessed by area under the receiver operating characteristic (AUROC) curve, which will be compared between each novel instrument and CAPS and APACHE II using the method of DeLong.[36]

Validation of prognostic tools

In the validation study: optimum thresholds chosen for categorisation of continuous variables used in the derived tool will be re-examined using the methods described above; and prognostic performance of the derived tool will be assessed by AUROC curve and compared to CAPS and APACHE II using the method of DeLong.

Subgroup Analysis:

Mortality and readmission rates will be compared by Fisher's Exact test in patients with, and without, predefined characteristics:

1. Late failure of NIV (recurrent respiratory acidaemia following initial correction, despite on-going ventilatory support)
2. Persistent hypercapnia (elevated arterial carbon dioxide level after weaning from ventilation, prior to discharge)
3. Long-term oxygen therapy.

4. Long-term ventilation on discharge
5. Eosinopenia <0.05 10^9/L on discharge

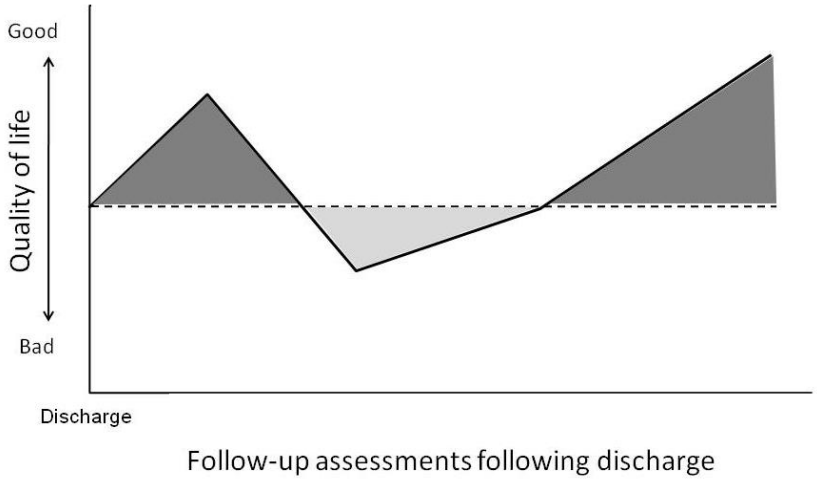
Times to readmission and mortality, stratified by the subgroups defined above, will be examined using survival analysis. Any significant relationships will be investigated for the effects of important potential prognostic confounders.

In patients with late failure of NIV, outcomes will also be compared to the historical Moretti [25] cohort.

Longitudinal study

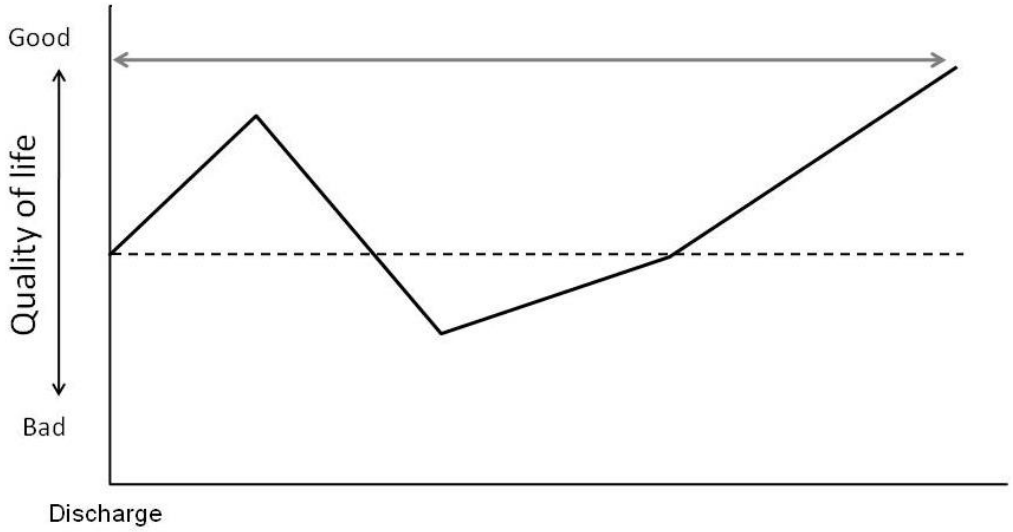
Data handling and descriptive methodologies described above will be used. We will use the following metrics to quantify longitudinal changes in patient reported outcomes including QoL (CAT, EQ-5D-5L); functional status (NEADL); and anxiety and depression (HADS):

1. Mean change in QoL, functional status and anxiety and depression scores: this provides a global measure of change over the entire follow up period. This can be compared to the MCID for each instrument to identify clinically significant results. Calculation of mean change is represented in the following graph.

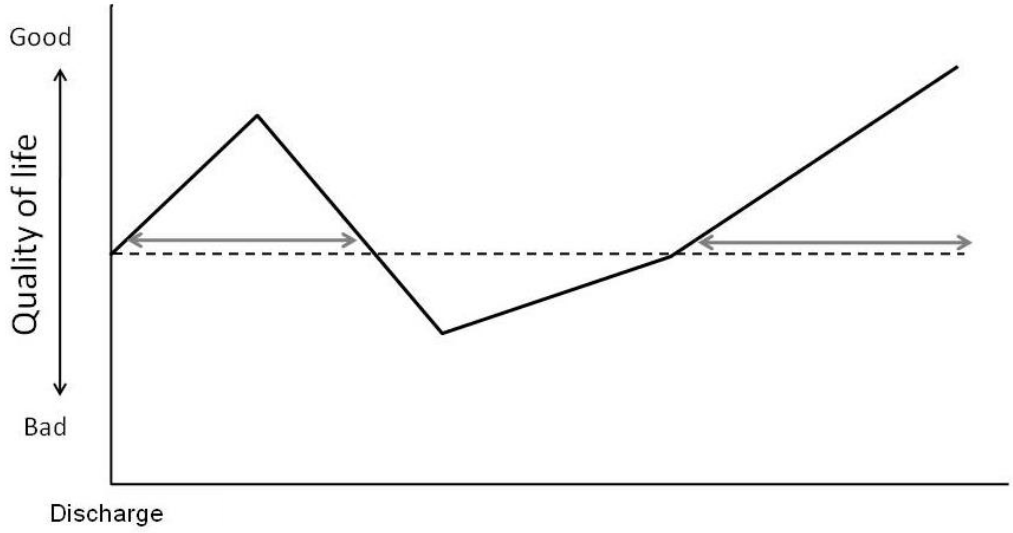


* Mean change in QoL = [area above the patient's baseline value (dark grey shading)] – [area below the patient's baseline value (light grey shading)] divided by length of follow-up.

2. Time taken to reach best recorded QoL, functional status, and anxiety and depression score: this will used as a measure of the time taken for the patient to recover following hospital discharge. This will also help identify those whose recovery is prolonged.



3. Duration score maintained above (better than) baseline: for patients with poor QoL or functional status at baseline, it is often a clinical concern that they may never significantly improve, and may even continue to deteriorate, and this assumption often influences clinical decisions. Similar concerns apply to anxiety and depression. The length of time spent with scores above (better than) the baseline level (grey arrows in figure below) provides a useful quantification of patient's subsequent experience that can be easily explained and understood.



We will assume that changes in scores for patient reported outcomes between assessments are related to time in rectilinear fashion. If a participant fails to attend a follow-up appointment but outcomes are recorded at the next scheduled visit, a time-adjusted average will be imputed for the missing value by assuming a linear change between the two data points either side of the missing assessment. If no follow up visits are attended, the individual will be excluded from analyses of longitudinal data. Similar to previous studies, for each questionnaire (except HADS) death will be equated to the score representing the worst status and, if a patient dies during follow up, a linear decrease will be assumed from the value at the last assessment to the time of death.

Individuals with a poor baseline QoL who experience a subsequent clinically significant decline in QoL will be defined as having a poor recovery. Predictors of poor recovery and 6-month survival will be identified using univariate analysis (as described above) followed by logistic regression analysis (backward stepwise methodology including non-collinear variables associated ($p<0.1$) with outcome) with 6-month survival and poor recovery as the dependent variables. The relationship between clinically significant anxiety and depression and survival, QoL, functional status and readmission rate will be examined using Fisher's exact test, Mann-Whitney U test, or Student's T-test depending on the distribution of the dependent variable.

Ethical Considerations:

To develop a meaningful predictive tool it is essential that patients at the extremes of mortality risk are not selectively excluded. The most unwell patients would be unlikely to be able to consent, introducing a significant selection bias were they to be excluded. All included indices are routinely available and participation will not influence normal clinical care. Mortality and readmission data is tracked electronically in all patients. The derivation study has not required individual patient consent (National Research Ethics Service 29/4/15, REC reference: 15/NW/0389, IRAS project ID 174869). All patients surviving to discharge will be invited to partake in a follow up study assessing patient reported QoL, anxiety, depression and functional status. This will require written informed patient consent. Ethical approval granted for the Validation/Longitudinal study: 11/7/16 REC reference: 16/NE/0213 IRAS project ID 206694.

Data Handling:

All data will be held securely on a password protected computer. Patients will be anonymously identified by an unique study number. It is necessary to be able to identify patients to follow up data queries or insert readmission data. A separate password protected computer will contain a database of patient demographics and their corresponding patient reference number. Transfer of data between internal and external sites will be via secure email.

Research Timetable and Management:

Ethical approval for the derivation has been obtained and data collection is underway. Data analysis is expected to begin early spring 2016 (this is not subject to this application). Following site selection and initiation, patient recruitment for the validation study will begin summer 2016 and run until spring 2018. During our pilot study we identified 199 patients in 18 months in our trust alone. As the study will be non-consenting recruiting 425 patients across a minimum of 6 sites in this timeframe is achievable.

Dr Stephen Bourke will act as chief investigator. He and Dr John Steer will co-supervise the research fellow Dr Tom Hartley who is undertaking a PhD through Newcastle University. Principal investigators including Dr Nick Hart will be responsible for local supervision at the respective validation sites. Statistical advice was sought in the development phase and ongoing support has been funded. Financial management, study sponsorship and data monitoring will be provided by Northumbria Healthcare NHS Foundation Trust R&D department.

Benefits of the Study:

Acute exacerbations of COPD requiring NIV are common with high mortality rates. NIV significantly improves outcomes, particularly when applied early. In the UK NIV is underused despite being widely available. Increasing appropriate NIV use will significantly improve survival rates. Enhanced outcome prediction is vital in encouraging increased NIV use.

We intend to provide an objective method of identifying patients who will benefit from NIV, enabling early identification and early initiation of therapy and challenging prognostic pessimism, which is pervasive in this condition. This will increase appropriate NIV use, which should improve survival rates.

Although effective, NIV can be difficult to tolerate. It can be claustrophobic, limit communication, and increase anxiety. Problems such as skin trauma and gastric insufflation may cause discomfort. If a patient has little chance of survival, alternative symptom based therapies may provide better end of life care than persevering with NIV. Therefore, a prognostic tool which accurately identifies patients with little chance of recovery could prevent undue suffering and allow timely palliative care.

At the time of clinical deterioration with respiratory acidaemia, patients are often too unwell to communicate their wishes and expectations. Treatment escalation plans, made at a point when the patient's condition is stable, can avoid rushed decision making at the time of deterioration when all relevant facts, including patient wishes, may not be available. This study will help inform clinicians, patients and carers and enable patient-centred treatment escalation planning thereby preventing poorly-informed decisions being made in emergency situations.

National recommendations on the management of late failure of NIV have a weak evidence base. Pilot data from our institution suggests that high intensity NIV has significantly better outcomes than the single study which informed the national guidance. If our pilot data conclusions are confirmed, guidance should be amended and, if adopted nationally, survival rates will improve.

Inpatient mortality should not be the sole arbitrator of whether an intervention is appropriate. Decisions should be informed by future survival, QoL and patient experience. Robustly investigating these components should allow for more holistic, patient centred, shared decision making.

Dissemination of Results:

The findings will be disseminated to a broad regional, national and international audience, including respiratory specialists, general physicians and intensive care physicians, through presentations at local, national and international conferences, and publication in high ranking, peer-reviewed, journals. Open access publication fees are included in our application.

Locally, we will keep patients, carers, primary and secondary care clinicians, healthcare managers, commissioners and neighbouring healthcare providers informed by publications in existing newsletters and presentations at local and regional meetings, conducted within both NHS organisations and the University. Through established links with the British Lung Foundation (BLF), we will seek to disseminate the results of the study through BLF electronic and published media. We will establish a patient/public group of service users and encourage them to publish the results from the perspective of patients and carers, facilitated by the research team and the BLF.

The research team and co-applicants include members (and the chair) of the UK NIV Research Network. We will keep the network and British Thoracic Society COPD Speciality Advisory Group (SAG) and clinical guideline groups informed about the progress and outcome of the study.

We will liaise with NHS Improving Quality; the scores developed could be implemented as part of a national service improvement project. A previous study conducted by our group describing the DECAF prognostic score was published in Thorax, awarded several international prizes recognising its importance and impact, and its use in clinical practice has been recommended by the recent National UK COPD Audit report. We expect similar success in the dissemination and clinical implementation of the results of the proposed study.

Research Team:

Dr Stephen Bourke, MBBCh (hons), PhD, FRCP. Consultant Respiratory Physician

Contact: North Tyneside General Hospital, Rake Lane North Shields, Tyne and Wear, NE29 8NH. Stephen.bourke@nhct.nhs.uk

Role: Chief investigator, trial design and supervision, data analysis and interpretation.

Relevant Expertise: Conception, design and delivery of the programme of research leading to development of the "DECAF" prognostic score, including derivation, external and internal validation and ongoing implementation studies. The latest National UK COPD Audit Report (Who Cares Matters; Feb 2015) recommends that the DECAF score should be performed in all patients admitted with AECOPD to inform clinical management. Stephen sits on the UK NIV Research Network and has gained strong support for the proposed trial including a surplus of volunteer sites. He has experience working across a variety of academic and commercial research studies. As Northumbria site PI in the recent HOT HMV trial he has worked closely with Dr Nick Hart. Stephen's programme of research investigating the role of NIV in motor neurone disease (amyotrophic lateral sclerosis) featured in Newcastle University Research Excellence Framework submission 2014 and includes a RCT (Lancet Neurol 2006) considered to be the seminal study in this area, influencing international practice. He was also involved in a recent RCT of diaphragmatic pacing in this condition (Lancet Neuro 2015), and guideline development and setting quality standards for the National Institute for Health and Care Excellence (NICE).

Dr John Steer, MBChB, PhD, MRCP. Consultant Respiratory Physician

Contact: North Tyneside General Hospital, Rake Lane North Shields, Tyne and Wear, NE29 8NH. John.steer@nhct.nhs.uk

Role: Co-investigator, input into trial design and supervision, data analysis and interpretation.

Relevant Experience: During his PhD studies John was the DECAF derivation study's PI. This work won two international prizes, was published in Thorax and was featured in the Thorax review of the year's influential papers. The similarities in research methodology and data analysis make this experience particularly pertinent.

Dr Nick Hart, MBBS (hons), BSc, PhD, MRCP Consultant Respiratory Physician, Clinical & Academic Director Lane Fox Unit

Contact: Lane Fox Unit, St Guy and Thomas' Hospital, Westminster Bridge Road, London, SE1 7EH Nicholas.Hart@gstt.nhs.uk

Role: PI in the St Thomas' site. Facilitate site recruitment. Contribution to data analysis and interpretation.

Relevant Expertise: Director of the Lane Fox Respiratory Unit (UK's national home complex ventilation and weaning centre) and the chair of the UK NIV Research Network, with extensive experience conducting clinical NIV research trials. He has worked extensively with the British Thoracic Society, the Royal College of physicians, NICE guideline development groups and the International COPD Coalition. Nick will act as principal investigator in St Thomas'. Amongst his large body of work he is chief investigator of the HOT HMV trial of NIV in patients with COPD.

Dr Tom Hartley, MBBS (hons), MRCP, research fellow

Contact: North Tyneside General Hospital, Rake Lane North Shields, Tyne and Wear, NE29 8NH. Tom.hartley@nhct.nhs.uk

Role: PI at Northumbria site, data monitoring, data analysis and interpretation.

Relevant Expertise: Tom is a respiratory specialist registrar taking time out of programme to deliver this research as part of his PhD studies.

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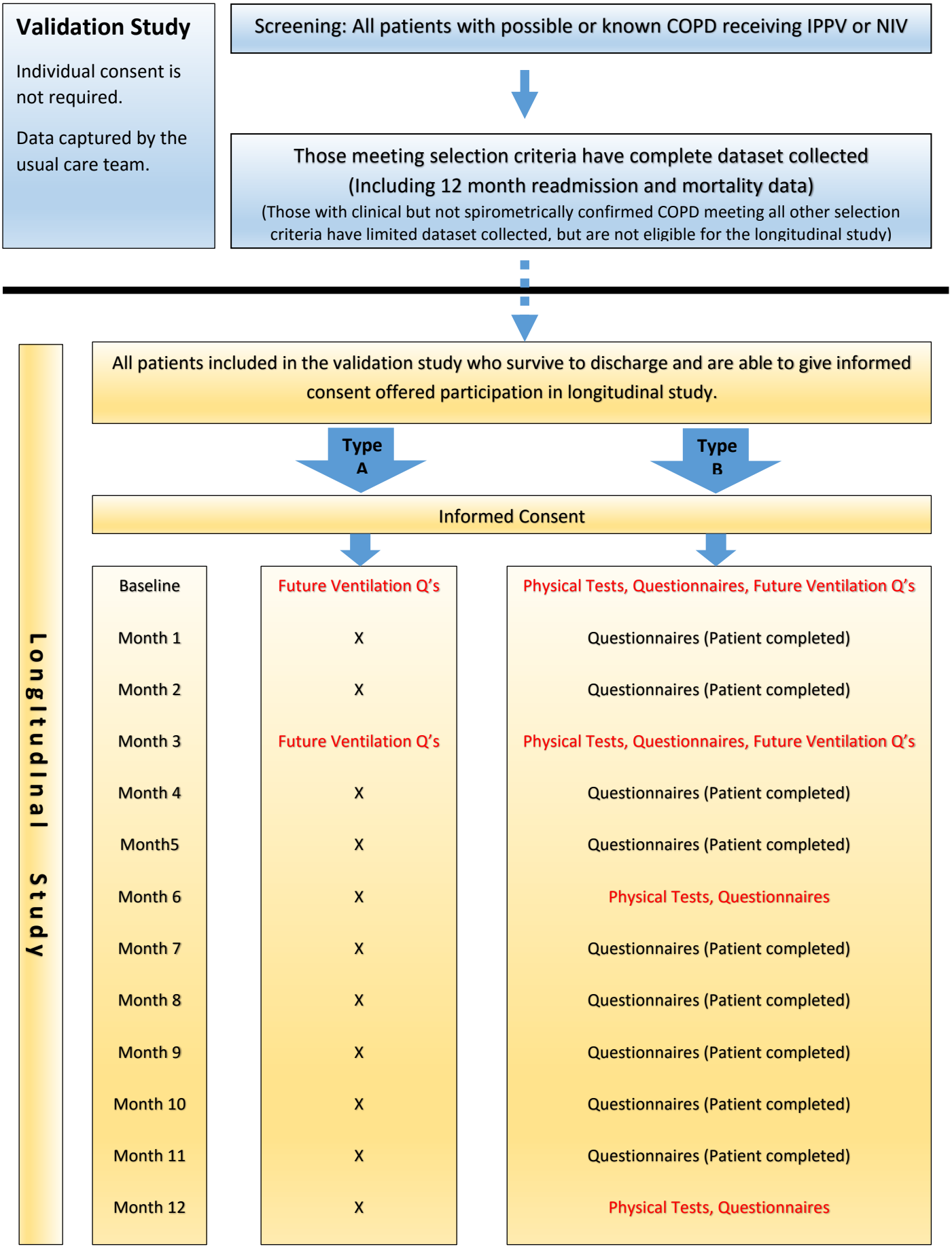
Appendix 1 flow diagram



Key: Red = Researcher face to face. Physical Tests = spirometry, weight, O2 Sats
Questionnaires = CAT, eMRCD, EQ 5D 5L, HADS, NEADL