Sefydliad Cenedlaethol ar gyfer Ymchwil Gofal Cymdeithasol ac Iechyd | National Institute for Social Care and Health Research

Llywodraeth Cymru
Welsh Government

National Institute for Social Care and Health Research (NISCHR)

Health Studentship Award 2014

Application form

Please refer to accompanying document *Guidance notes for completing the application form* when completing this application form.

SECTION A: Applicant Details

1. Project details

1) Title of project

Novel methods for identifying the disease modifying potential of pulmonary rehabilitation in chronic obstructive pulmonary disease

2. Applicant details

Name:	Arwel Wyn Jones
Current job title:	Postdoctoral researcher
Institution:	Aberystwyth University and Hywel Dda University Health Board
Contact address:	F.25, Carwyn James Building, Penglais Campus, SY23 3FD
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Name:	Luis Mur
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Name:	Keir Lewis
Job title:	Associate Professor
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3. Host Institution details

Host Institution:	Institute of Human Sciences, Aberystwyth University
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SECTION B: Project Details

4. Cost and duration

Please enter the total cost of your project to NISCHR:

£65,988

Start date: *1st October 2014*
Expected thesis submission date: On or before September 30th 2017

5. Lay summary (word limit: 300):

Chronic Obstructive Pulmonary Disease (COPD) is a progressive debilitating condition caused mainly by smoking and is now the third largest cause of death worldwide. It is also the second most common reason for hospital admission in the UK, costing the NHS over £1 billion each year in direct costs alone. Pulmonary rehabilitation (PR) is a programme of supervised core aerobic exercise and patient education over 6-12 weeks. It is one of the most effective and cost-effective interventions for COPD by reducing time in hospital, increasing exercise capacity, independence and improving quality of life. However, there are urgent calls from the Welsh Assembly, Lung Charities (British Lung Foundation) and the Welsh and British Thoracic Societies to better understand why not all people with COPD benefit from PR and why and how quickly the positive gains fade over time. As our burden of COPD increases, through an ageing population and limited NHS resources, more work is needed to predict PR responders, provide better support for more vulnerable PR participants, optimise the exercise regimes and determine the optimal duration of PR. Our published studies in the last 5 years, show novel technologies (e.g. Fourier Transform InfraRed Spectroscopy and Mass Spectroscopy) developed in our University can distinguish sputum samples from people with COPD from healthy controls and lung cancer patients. Now we want to apply a greater array of these same technologies to blood biomarkers (metabolites, proteins) of people enrolled in PR and relate these measurements with clinical outcomes. We will better understand why patients respond differently to PR and simultaneously compare responses to two established PR programmes in Wales, of different duration. These results will identify specific biological responses to exercise in those suffering with chronic lung disease and could help tailor PR programmes for maximum and maintained gains in the future.

6. Keywords

Keywords: COPD, exercise, biomarker, metabolomics, proteomics

7. Priority policy area(s)

7a) Please indicate which of the priority areas below your project addresses: (more than one option may be ticked)

- Prevention and early intervention ☒
- Chronic conditions management ☑
- Service organisation and delivery ☑ (Delete as appropriate)

7b) Please describe how the proposed research addresses the policy area(s) indicated above (word limit: 300):

Wales faces a serious challenge of an increasing older population with greater health inequalities, reduced NHS resources with a higher than UK average prevalence of chronic diseases. Research is required urgently for better management of chronic conditions to achieve sustainable health and social care in Wales.

COPD is a preventable and treatable but progressive, chronic inflammatory lung condition affecting many other parts of the body. Population surveys suggest up 3.5 million people have symptoms of COPD but only 1.2 million are registered (the 'Missing Millions' – British Lung Foundation 2010). In 2009, COPD had direct UK healthcare costs of £810-£930M per annum, of which £700M was spent on hospitalisations. Indirect costs of COPD are massive, approximating to 24 million lost working days per annum.

Pulmonary rehabilitation (PR) helps to prevent and/or manage many of the debilitating effects of COPD for an individual and saves the NHS around £700 for every patient enrolled (Griffiths, 2000) so is recommended in all National and International Guidelines for COPD. By using new technologies to maximise PR, this research aligns with the Integrated Model and Framework for Action for Chronic Conditions in Wales to "improve health interventions and promote holistic management and design of graduated and integrated services involving a multidisciplinary team to provide evidence based care pathways." The proposed research conforms to the Welsh Government objectives of "Healthy lifestyles/Healthy aging" for better design of services to ultimately limit the progression and maintain quality of life of those members of our community living and dying with one of our most common chronic conditions.

This project adopts the philosophy of the Welsh document 'Together for Health' by helping develop "robust evidence on currently available cost effective treatments and optimise the efficacy of these resources to ensure the best outcomes for patients and service users."

8. Need and impact (word limit: 300)

COPD results in a major societal and economic burden. The UK Database of Uncertainties about the Effects of Treatments (UK DUETs) of the National Institute of Health and Care Excellence (NICE) have published specific recommendations (based on systematic reviews of the evidence base, Beauchamp et al., 2011; Kruis et al., 2013) for further research in integrated disease management interventions for COPD[1] and an investigation of the optimal duration of PR[2] for individuals with COPD.

Current PR programmes are integral for people with COPD as it is based on robust, Grade A evidence. For example, the estimated health care costs per patient decrease by more than 50% following PR. Rising demands in prescriptions and elevations in ineffective treatment options (e.g. steroids or antibiotics in antimicrobial resistance) warrant further use of these proven interventions such as multidisciplinary PR that target the multi-systemic illness of COPD. Despite this strong evidence, PR remains patchy and inconsistent in Wales, often with long waiting lists even where it is offered regularly. This partly reflects some unanswered scientific questions about how best to structure PR for more efficient delivery (e.g. optimise impact, reduce cost of provision).

Personalisation of PR should allow better disease-modifying potential. Using new (and cheap) technologies to identify biomarkers to get better selection of patients, optimise exercise components and duration would make PR much more efficient within a few years.

1.http://www.library.nhs.uk/duets/ViewResource.aspx?resID=416711&tabID=297&catID=15581

2 http://www.library.nhs.uk/duets/ViewResource.aspx?resID=411749&tabID=297&catID=15581

9. Timetables and milestones

Please give an indicative timetable for the project including key milestones and outputs *(please add more rows as necessary)*

Date	Milestones and outputs	
August 2014	Student recruitment	
October 2014	Start of project	Thesis chapter development
October 2014 - February 2015	- Completion of venepuncture training, relevant NISCHR courses (e.g. good laboratory practice) - Completion of ethical approval and start of recruitment of patients referred to pulmonary rehabilitation patients	
June 2017	Completion of data collection	
June 2017- September 2017	Completion of any remaining data analyses (i.e. statistics) and/or thesis write-up	
September 2017	Thesis submission deadline	

10. Detailed project description (word limit: 3000)

10.1 Background (existing research)

Rigorous evidence from randomised controlled trials demonstrates that multi-disciplinary interventions such as pulmonary rehabilitation (PR) programmes of 6-12 weeks for COPD can improve dyspnoea, exercise tolerance, HRQL, and reduce the number of days spent in hospital and the utilisation of healthcare resources (NICE, 2011; Nici et al., 2006; Ries, 2008, Griffiths et al., 2000, 2001). PR programmes are now recommended for all COPD patients who remain limited by their chest despite optimal pharmaceutical treatments, irrespective of severity and age (Bolton et al., 2013; GOLD, 2013).

Cardiff and Vale University Health Board (UHB) (Llandough Hospital) and Hywel Dda UHB have two of the most established PR programmes in Wales. They both treat symptomatic patients with COPD for 3 sessions per week for 6 weeks or 2 sessions per week for 9 weeks respectively. Based on our previous research, these programmes result in comparable clinically important average improvements in standard PR outcomes (e.g. increase in incremental shuttle walk test (ISMWT) distance, Health Related Quality of Life (HRQL) and less days in hospital) (Lewis et al., 2012). However, not everyone completes or benefits from PR. A better understanding of underlying mechanisms for improvement would allow us to tailor PR and hopefully prevent the typical decline back towards baseline values upon completion of PR seen 6-12 months later (Spruit et al., 2013).

HRQL benefits appear to better preserved following PR than exercise performance, possibly because of greater illness understanding and personal confidence. Maintaining the gain of PR is vital given PR is targeting

a disease that causes an accelerated physiological decline over time. Repeat PR is considered to be one strategy that could maintain the benefits of the initial programme by encouraging exercise maintenance. Repeated PR is associated with fewer exacerbations and fewer days in hospital but the gains in exercise capacity and psychometric outcomes may not be as large as the initial programme. The most recent BTS PR guideline (Bolton et al., 2013) explicitly calls for further research to determine the optimal selection for any repeat PR.

There is also a lack of evidence to explain the great variation in patient responses to PR. Traditional clinical parameters (e.g. severity of lung function) do not accurately predict outcome. Although the exercise component of PR exerts numerous beneficial effects, the degree of benefit (e.g. in exercise tolerance) is dependent on other modifiable factors (e.g. nutritional deficiencies). Despite these recognitions, the BTS PR guideline has highlighted that biological response to exercise in COPD remains an underexplored field. The recent American Thoracic Society / European Respiratory Society statement (Spruit et al., 2013) has called for researchers to improve "the understanding of the heterogeneity and complexity of COPD in order to define patient phenotypes which can be used to optimise the impact of PR".

We have shown that metabolomics provides a robust 'global metabolic snapshot' of the system under investigation by simultaneously determining as many metabolites as possible without bias towards any particular group (Jones et al., 2013; Lewis et al., 2010; Mur et al., 2008). Metabolomics approaches are increasingly used in clinical medicine, mainly in biomarker discovery (Monterio et al., 2013). An integrated approach of high-end technology (metabolomics) and clinical outcomes will improve understanding of the underlying mechanisms contributing to COPD progression (Kelly et al., 2013). Metabolomics allows for the investigation of the interplay between genomic and post-transcriptional mechanisms that modulate physiological adaptations to the environment (i.e. treatment) and thus influence phenotypic parameters (Holmes et al. 2008). For example, metabolomics profiling has demonstrated that unlike homogenous responses to training in healthy participants, people with COPD have very heterogeneous responses, resulting in a lack of training response in some individuals (Rodriguez et al., 2012). Metabolomic profiling also allows all time points within a study to be normalised against a baseline measure, to determine each individual's metabolic response over time as well as a reliable comparison of response to treatment between individuals (Chorrel et al., 2009).

In proteomic approaches the entire complement of proteins produced by an organism or a cellular system are characterised. Within the context of COPD, proteomic analyses of some sample types (e.g. sputum) have already suggested biomarkers for diagnosis, therapy, and prognosis. However, serum remains a relatively unexplored as a source of peptide biomarkers linked to COPD (Chen et al., 2010). Combining metabolomics with proteomics can provide further detailed separation of responses than single 'omics platforms by providing a clear picture of both short-term and long-term adaptations to treatment (i.e. PR).

10.2 Aims and objectives

The larger objectives of this and our ongoing collaborations are to develop expertise in COPD research in Wales to generate scientific discoveries on disease mechanisms and phenotypic biomarkers that will lead to improved and individualised disease management strategies. The project intends to contribute to this by:

1. Performing metabolomic and proteomic analysis of blood (sera and plasma) that will provide insights into primary metabolism and how different durations or structure of PR influence important pathways in inflammation (e.g. cytokine and eicosanoid profiles) and hence disease severity.
2. Deliver predictive biomarkers alongside clinical parameters (exercise capacity, HRQL) to define clinical phenotypes based on which the relative merits of COPD PR regimes can be designed to meet the requirements of a given patient.

10.3 Design and method

This project will build on continuing links (previous NISCHR grant and joint post-doc appointments) between the Hywel Dda UHB and Aberystwyth University by conducting a longitudinal, prospective investigation of COPD patients referred to PR. There are strong links also between the clinicians in the PR settings of Hywel Dda and Cardiff and Vale UHB with established track records of joint publications.

10.3.1 Participants

Ethical and R&D permissions will be sought prior to participant recruitment. We will also seek adoption for study onto the Welsh Portfolio. People with confirmed, stable and optimised COPD are referred for consideration of PR according to standard criteria (BTS 2013, Griffiths et al., 2000). Following PR referral, participants will be contacted via letter (addressed from both the health boards and Aberystwyth University) and offered participant information sheets. As per service guidelines, we will not include anyone with an inability to walk, symptomatic unstable ischaemic heart disease and severe sensory or cognitive impairment preventing them to follow simple commands during PR.

10.3 2 Pulmonary rehabilitation

Patients at each site (i.e. at hospitals of Hywel Dda or Llandough Hospital) will be referred into the conventional PR programmes. Each programme is designed to accommodate 8-12 patients. The total number of patients referred to PR at these sites equates to over 320 over 3 years. Allowing for non-completion, deaths and other losses to follow-up, we expect to report longitudinal outcomes on 160 patients.

The PR Programmes in Hywel Dda and Cardiff and Vale UHB are similar (total number of sessions - 18, identical content, order and assessment format) and have been described elsewhere (Griffiths et al., 2001, 2002; Lewis et al., 2012; Sabit and Lewis et al., 2008). Each session lasts for

approximately 2.5 h starting with supervised, individual exercise, consisting of lower extremity training (treadmill, step-ups) and upper extremity training (resistance bands and loose weights). This is followed by group educational activities, addressing the causes and types of lung disease and psychological aspects of chronic disability. Individual goal setting, dietetics, physiotherapy and occupational therapy are also included.

Participants at both health boards will be randomised to a follow up of usual care or a 'top-up' consisting of repeated supervised exercise for 1-2 hours, in hospital, twice weekly for 2 weeks at 26 weeks (six months) following the initial programme (Figure 1). Patients not randomised to the repeated programmes (i.e. usual care) will be asked to attend the hospital to collect standard clinical outcomes at baseline, 12 weeks (3 month follow up), 26 weeks (6 months follow up) and 52 weeks (12 months follow up) (Figure 1). Patients randomised to repeated PR will be asked to attend the hospital to collect standard clinical outcomes at baseline, 12 weeks, 26 and 28 weeks (pre and post repeat PR) and at 52 weeks (Figure 1).

These standard clinical outcomes include: ISWT, psychometric measures (COPD Assessment Test (CAT) Questionnaire, Hospital Anxiety and Depression Inventory), number of hospital admissions, number of days spent in hospital. The CAT (Jones et al., 2009) is a simple 8 question, robust tool developed from the St Georges Respiratory Questionnaire (Jones, 1992) that is being increasingly used in COPD to assess effectiveness of health interventions. Anxiety and depression will be measured using the Hospital Anxiety and Depression Inventory (HADS; Zigmond and Snaith, 1983). The questionnaire comprises 14-items consisting of two separately scored subscales that measure anxiety and depression. Using a 4-point response scale, participants indicate how regularly in the past week they have experienced specific feelings, with scores ranging from 0-21).

As evaluation of factors which influence changes in the risk of exacerbations (worsening of symptom severity beyond day to day variation) is a focus of another PhD studentship (supervised by Prof. Luis Mur, Dr. Keir Lewis and Dr. Arwel Jones, start date: September 2014) and such acute events represent the greatest burden for patients and health care, frequency of exacerbations in comparison to pre-PR will also be recorded at follow up timepoints.

10.3.3 Blood collection

Alongside the standard clinical outcomes (upon referral to initial PR i.e. baseline, follow up timepoints and/or pre and post repeated PR), the student will arrange, collect (venepuncture), centrifuge and store blood samples (as plasma and serum) for later metabolomics and proteomics profiling (Figure 1).

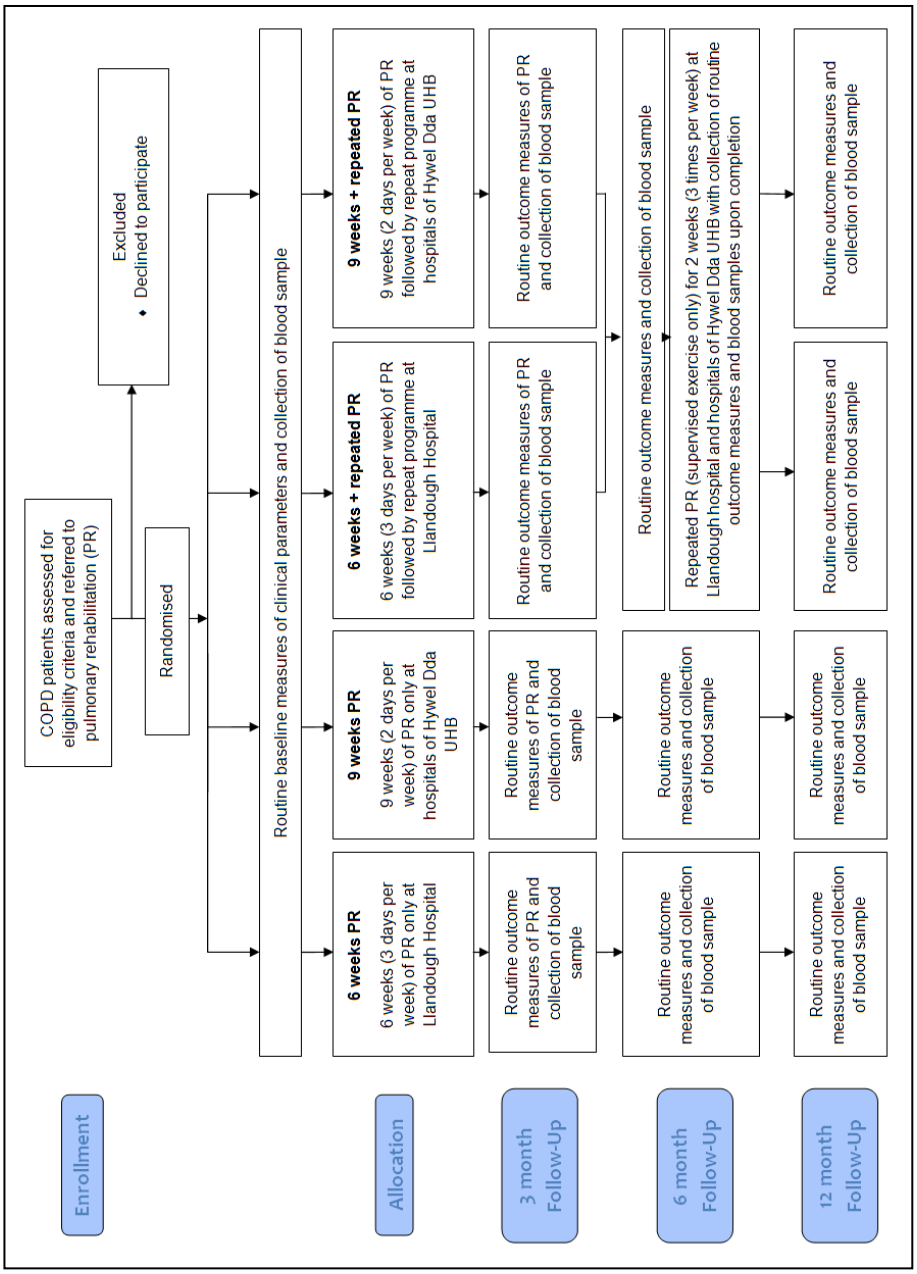

Figure 1. Schematic outline of the proposed project.
PR – Pulmonary rehabilitation; UHB – University Health Board

10.4 Use of resources

All analyses will exploit the expertise and make use of equipment and methodology (detailed in method of analysis) already developed at the sites of the research team:

Dr. Arwel Jones[1] (exercise and nutritional immunology); Prof. Luis Mur[2] (metabolomics and proteomics); Dr. Rachel Rahman[1] (health psychology); Dr. Les Tumilty[1] (central fatigue)

[1] Institute of Human Sciences, Aberystwyth University
[2] Institute of Biological Environmental and Rural Sciences, Aberystwyth University

The protocol also has the full support of lead Respiratory Consultants involved in referral of patients to PR at both health boards.

Dr. Keir Lewis (clinical biomarker research, R&D Director and Clinical Lead for PR)[1]; Dr. Ramsey Sabit (Clinical Lead for PR)[2]

[1] Prince Phillip Hospital, Llanelli
[2] Llandough Hospital, Cardiff

Consumables costs for blood collection (e.g. vacutainers, needles, £800) at hospital sites and analysis for metabolomics/proteomics (standards, reagents - £5000) at the Mur Lab have been estimated on the expected patient referral and follow up (outlined in section 10.3.2, Figure 1). The student will have a wet-bench available in the Clinical Research Centre, Prince Philip Hospital and consumables will also be supported from Dr Lewis's Research Fund). Travel and subsistence costs proposed by this project include attendance of student at one international (American Thoracic Society) and UK based scientific meeting/conference (e.g. Welsh Thoracic Society) (year 3). Given the rural setting of this project, costs have also been allocated on a yearly basis to reimburse student for attendance to hospital sites for collection of blood samples.

Although internal continual professional development (see section 14) and relevant NISCHR courses (e.g. good laboratory practice, GCP) would be available at no cost to the student, costs have been allocated for venepuncture training (i.e. phlebotomy course) in year 1. The student will be mentored for the development of this technique by members of the supervisory team, trained in venepuncture (Dr. Arwel Jones, Dr. Keir Lewis).

10.5 Method of analysis

10.5.1 Blood analysis (metabolomics and proteomics)

Individual serum and plasma samples will be split and separately analysed following metabolomic and proteomic protocols to determine changes in response to duration of PR (six/nine weeks) and/or repeated PR. Metabolomic samples will be assessed via a hierarchy of Mass Spectrometry (MS) platforms available to the Mur Group. Initial profiling will employ Liquid Chromatography and Gas Chromatography (LC – and GC-MS). Metabolite profiles would be analysed using accepted Metabolomics Standard Initiative procedures (Sansone et al., 2007). Heat-mapping, hierarchical cluster analysis and preliminary univariate statistical analysis would be completed on the metabolomic data with multivariate feature selecting algorithms including principal component analysis, random forest and supervised (where key variables are determined using a priori defined groups) approaches including Discriminant Function Analysis and the use of "genetic algorithm. Analyses will be based on generic statistical software – particularly R and Mat Lab but also bespoke metabolomic analysis software. Following statistical analyses, tentative identification of metabolites of interest would be achieved through interrogation of the Human Metabolome Database (Wishart et al., 2009). Confirmation of metabolites will involve high-resolution MS based on single-stage Orbitrap coupled with fragmentation patterns generated by tandem MS. Our analyses will include

the use of standards for 1) plasma amino acids- tyrosine, phenylalanine, leucine, isoleucine, valine, free-tryptophan, methionine, threonine, histidine and 2) a profile of arachidonate-derived eicosanoids concentrating on the prostaglandins (to PGE2, PGI2, PGD2, PGF2α, and TXA2) to allow accurate measurements for these targeted metabolites to be obtained for each sample.

Serum will be profiled for small peptides. Protein extracts are digested directly with trypsin in solution to give a complex peptide digest. To achieve peptide quantification, the digests will be labelled with ITRAQ. Peptide fractions will be fractionate on a Triple quadrupole MS which is dedicated only to proteomic studies. The first quadrupole allows the peptide profiling whilst the second acts to fragment the peptides so that sequence data can be obtained via the third quadruple. Protein identification is achieved using MASCOT search tools on in house computers searching all publicly available databases. We propose to accurately quantify interleukins (particularly IL-1 and TNF) and interferon (IFN1) through comparisons with standards in each sample.

10.5.2 Clinical outcomes

The student will have an NHS research passport and honorary contract with Hywel Dda UHB, under the clinical supervision of Dr Keir Lewis. The PR delivery teams from both health boards have experience in working with researchers and broadly welcome this project. The student will also work closely with established physiologist/psychologist teams at Aberystwyth University (see above) for the interpretation of psychometric measures and interpretation of clinical data. Changes in clinical outcomes with the six and nine week PR will be analysed in accordance with our previous work (Lewis et al., 2012). Statistical analysis of this data will be performed via the statistical computer software package SPSS (v21.00 or later version; SPSS Inc., Chicago, IL, USA). For example, pre to post (PR) changes in clinical outcomes between these programmes will be assessed using Analysis of Covariance (ANCOVA) or non-parametric equivalent. Correlations and mediation analysis will also be used to explore relationships between metabolite/protein data and clinical outcomes to determine if, and to what extent, PR may mediate the impact on clinical outcomes (e.g. exercise capacity, quality of life) on a metabolic and protein level.

Due to the expected number of patients that would be referred to PR during the timescale of the project and the high mortality rate associated with the proposed population (hence lost to follow up), the *priori* intention with the analyses of repeated PR will be to assess its feasibility. Our interpretation of results will therefore be focused on point estimates and precision, rather than the statistical significance between usual care and repeated PR. Feasibility will be assessed by considering the clinical importance of differences observed within the confidence interval, interpreted in the light of the process outcomes and the implications for future research/healthcare use. The point estimates, range and SD of outcome measures, participant adherence and willingness of participants to be randomised to repeated programmes will all be considered in the evaluation of repeated PR.

10.6. Expected outcomes and impact

10.6.1 Expected outcomes and impact (Aims and objective 1)

Metabolomic and proteomic analysis at a systemic level will provide greater understanding of pathways important in inflammation and disease severity in COPD patients. The novel approach of metabolomics/proteomics will expand on the efficacy and mechanisms of PR in a COPD population following its pre-established proof of concept. It will identify the effectiveness of varying durations of PR and support judgement on the usefulness of modifying the delivery (i.e. repeated programmes) of PR from a systems biology perspective rather than exercise capacity and psychometric measures only. For example, it may suggest whether repeated programmes are beneficial for all patients or certain sub groups e.g. those individuals who suffer from frequent exacerbations. Determining the effects of PR on inflammatory pathways would also provide important evidence regarding how PR would be best applied at stages of disease other than the stable state (e.g. post hospitalisation). Such targeted treatment would provide better management of condition and likely confer a general reduction hospital, all of which reduces the economic burden of prescription costs to the NHS.

10.6.2 Expected outcomes and impact (Aims and objective 2)

The project will elucidate the underlying mechanisms (metabolic and proteomic changes) of responding/ non-responding patients to PR treatment. At present in these health boards, patient responses are classified by respiratory consultants according the following criteria:

- *Immediate good responder***:** Patient who has a statistically significant and clinically meaningful improvement in HRQL and ISWT immediately post PR
- *Medium term good responder:* Patient who has maintained a statistically significant and clinically meaningful improvement in HRQL, ISWT at 26 weeks (6 months) and spent less days in hospital than the preceding 26 weeks before PR.
- *Long-term good responder*: Patient who has maintained a statistically significant and clinically meaningful improvement in HRQL, ISWT at 52 weeks (12 moths) and spent less days in hospital than the preceding 52 weeks before PR.

Assessment of phenotypic markers (i.e. metabolomics) alongside these classifications will allow for individual components of programmes to be manipulated and/or identify targeted adjunct interventions to optimise PR outcomes in those patients lacking medium/long term adaptations. For example, patients suffering from chronic inflammatory conditions are often at greater risk of symptoms such as fatigue and depression and this is thought to involve altered metabolism of the brain neurotransmitter dopamine (Brydon et al, 2008; Capuron et al., 2007; Juengling et al., 2000). The blood ratio of phenylalanine/tyrosine has been adopted as an indirect marker of central dopamine function in cancer patients (Felger et al., 2013; Neurater et al., 2008) and is likely to be a potential peripheral marker of

fatigue in COPD patients. Targeting nutritional interventions to modify this amino acid balance would be expected to improve exercise capacity (by alleviating a barrier to exercise completion i.e. fatigue) and HRQL.

10.7 Dissemination

As the collective aim of this project will be to generate scientific discoveries on mechanisms and phenotypic biomarkers of COPD, one of the major areas of dissemination will be scientific publications in high impact journals. Given the nature of the proposed work to perform measurements on actual patient-centred outcomes under real world conditions, the evidence gathered and protocol will be disseminated to the BTS PR guideline development group which act on behalf of the BTS standards of care committee. As mentioned previously (section 10.5.2), this project will also provide novel evidence regarding the feasibility of repeated PR in a COPD population. Thus the project will allow progress of the area towards larger clinical trials whereby health care professionals can make more informed decisions regarding patient management and care pathways.

The proposed project on COPD will also complement a recent EU award looking at telehealth interventions and self-management of COPD at the Clinical Research Centre of Prince Phillip Hospital. Having researchers working within the same health board will allow cross-fertilisation of ideas and future collaborations where biomedical tests to identify those at high risk of hospitalisations could allow most efficient use of limited resources in telehealth monitoring to support and maintain the most vulnerable in their own environment. In order to maximise awareness and impact of the research hence target all relevant stakeholders, findings will be disseminated to relevant charities including their respective local support groups (e.g. Breathe Easy, British Lung Foundation). This would support a patient centred approach upon project completion and attempt to provide long lasting engagement in PR and highlight the positive impact of health research within the COPD population.

11. Ethical considerations and approval (word limit: 300)

Research Ethics Committee Permission will be obtained following review by the Hywel Dda Health Board R&D Research Review Panel.

This project will be conducted in accordance with the ethical principles stated in the most recent version of the Declaration of Helsinki or the applicable guidelines on good clinical practice; whichever represents the greater protection of the individual. All patients involved in the study will be provided with an information sheet and have the opportunity to discuss the study with member of the research team prior to providing written informed consent. The decision of the patient about whether or not to participate in the study will have no bearing on their eligibility to attend the PR and will not affect the quality of their care in any way. Participants will be free to withdraw from any aspect of the study at any point without any impact on their attendance at PR.

All samples will be collected and stored anonymously in accordance with

the study protocol and previously developed standard operating procedures and risk assessments at respective sites. Psychometric data will be stored in a locked filing cabinet at Aberystwyth University and will be allocated participant IDs to ensure anonymity.

12. Patient and Public Involvement (PPI) (word limit: 400)

The Department has a demonstrable track-record of engaging key stakeholders in its research projects, and in organising and hosting events that promote patient and public involvement, e.g. the Age Agenda in Aberystwyth (June 2011)[1], Preventing Harm from Falls (Oct 2012)[2], and the Mid-Wales Diabetes Information Evenings (running quarterly since March 2011)[3]. The supervisory team not only recognises the added value of user involvement in all stages of research, but will also be able to draw upon the Department's extensive experience in this regard to ensure the project meets quality standards for appropriate patient and public involvement. Patient feedback from an existing portfolio study, Medlung (UKCRN 4682) and a pilot study (REC reference number:10/WMW01/30) at the Clinical Research Centre (Prince Phillip Hospital, Hywel Dda) has also contributed to the development of the protocol. Our research and recording of patient's experiences and their design into our PR programmes is also available[4].

If funded, the supervisory team will convene a Project Steering Group. The Involving People Network has been contacted regarding this research and we will be looking to involve patients with COPD (who have and have not previously completed pulmonary rehbailiation programmes). We will utilise our membership of the Ceredigion Older Peoples Partnership to ensure adequate patient and public involvment at each phase of the project. Initially, involvement will be especially important for the contextualisation of the project and the development of participant information sheets and consent forms. If appropriate, we will encourage patient and public involvement in the presentation of findings at relevant stakeholder meetings. The proposed project structure will enable early and ongoing contribution to the research process by those for whom such a service, if effective and cost-effective, would be intended for and provided.

1. http://www.aber.ac.uk/en/news/archive/2011/06/title-99845-en.html
2. http://www.wales.nhs.uk/sitesplus/862/news/22941
3. http://www.aber.ac.uk/en/sport-exercise/latest-news/newsarticle/title117235-en.html
4. Hutchings, H. A., Rapport, F. L., Wright, S., Doel, M. and Lewis, K. E. (2014) Nominal Group Technique consultation of a Pulmonary Rehabilitation Programme [http://f1000r.es/] F1000Research : (doi: N/Af1000research.N/A-N/A.v1)

13. Other applications for funding

Date submitted	Funding body	Title	Value	Date outcome will be known

SECTION C: Institution details

14a. Departmental performance rating in most recent Research Assessment Exercise (RAE)

Unit of Assessment	Staff Submitted (FTE)	By percentage, research activity in the submission judged to reach quality standard				
		4*	3*	2*	1*	UC
Sports-Related Studies[1]	8	0%	15%	50%	35%	0%
Agricultural, Veterinary and Food Science[2]	46.5	10%	35%	50%	5%	0%
[1]Primary Host Department; [2]Secondary Host Department						

14b. Supporting information (word limit: 200)

The current application builds upon, and strengthens existing collaborative partnerships between the Department of Sport and Exercise Science (Institute of Human Sciences, Primary Host) and Institute of Biological, Environmental and Rural Sciences (Secondary Host) of Aberystwyth University.

Research has been a core activity of the Primary Host Department since being established in 2002. Submission to RAE 2008 was based on the research activity of 8.0FTEs, four of whom were early career researchers (ECRs). Since 2008, we have continued to invest strongly in academic staff, postgraduate researchers (PGRs) and research infrastructure.

Submission to REF 2014 included 12.2FTEs, three of whom were ECRs. We estimate, based on external assessment, that $\geq$30% of our research outputs will achieve $\geq$3* quality rating. In addition to academic staff, the Department comprises 10 PGRs, three postdoctoral research fellows and three technicians.

The Department continues to build capacity around a portfolio of research focussed on physical activity, rehabilitation and health in older people and people with chronic conditions. Funding for current projects involving staff, as either PI or Co-I, total more than £4,000,000, including the Prevention of Fall Injury Trial (NIHR £2.4m: ISRCTN71002650) and Dementia And Physical Activity (NIHR £1.4m: ISRCTN32612072).

15. Contribution and track record of the PhD Supervisor (word limit: 300)

Dr. Arwel Jones is an early career researcher whose work has included applying metabolomics to assess the effect of nutritional interventions on human metabolism (inflammatory responses). AJ, with his letter of access for research in the NHS, is developing bioassays (not routinely avaible) for COPD with the Clinical Research Centre (CRC) of Prince Phillip Hospital (PPH) in order to provide biomarkers that reflect disease severity. AJ currently mentors one MPhil researcher investigating the effect of exercise on inflammatory responses in COPD patients who have undergone pulmonary rehabilitation. AJ's experience of engagement with research participants (clinical/non-clinical) in experimental and longitudinal trials will be integral in advising the student on blood collection and analytic procedures in the laboratory.

Supporting AJ in managing the project and leading the supervision of the student will be senior colleagues Prof Luis Mur and Dr Keir Lewis. LM will lead parts of the project involving the measurements of pro-inflammatory factors and circulating amino acids involving metabolomics and proteomic approaches. LM will supervise the use of data-mining strategies to target key features using statistical and machine learning approaches. To support this work, LM will use his expertise in Mass Spectrometry and the analysis of complex datasets; an expertise that is attested by his publication record.

Support for the student will be provided as required, as well as through formal arrangements that include a regular supervision meeting with AJ (initially fortnightly), a monthly meeting with the Aberystwyth University supervisory team (AJ and LM) and a quarterly meeting with the Director of Postgraduate Studies.

Dr Lewis, is a Clinical Academic with an interest in biomarkers and COPD. He runs a specialist COPD clinic, developed the business case for pulmonary rehabilitation and smoking cessation services. As R&D Director in Hywel Dda, KL heads the CRC in PPH and will identify and help recruit patents and supervise clinical environment, including leading on R&D and ethics permissions.

16. Training and development (word limit: 300)

A strategic aim for the Department is to increase numbers and quality of our Postgraduate research student cohort – currently 10 doctoral students with 4 progressing this year from MPhil to PhD registration. Development of postgraduate training in the Department is driven by the RCUK Researcher Development Framework (2011), and the QAA Code of Practice for Postgraduate Research Programmes (2004). Our aim is to provide training in multi-disciplinary research and to facilitate development of transferable skills to suitably equip modern applied health researchers.

In line with the university-wide CPD compact, research students undertake an annual training needs assessment with their supervisory team, identifying their generalist and specialist needs, to generate an individual development plan maximising their benefit from the diversity of AU-based training opportunities. Students are required to review and report on their progress periodically as part of the progression process.

Training continues throughout the PhD as the students' needs change, e.g. initially to develop understanding of project design, ethics and intellectual property; later to develop communication and writing skills, and careers development; latterly to develop publication and funding skills. In addition, the Graduate School runs its own quality-assured courses in four key skills clusters that map to the RCUK Researcher Development Framework: (1) Research Management, (2) Communication Skills, (3) IT, and (4) Career and Personal Development.

The Department's policy is to allow Postgraduates a period equivalent to two weeks per year to under-take training and development of various forms, including seminars, workshops and residential training courses. Research students are encouraged to engage fully in the Department's research culture, e.g. participation in our fortnightly research seminar series. Following successful progression at 12 months, Postgraduates are encouraged to take advantage of teaching opportunities, but this must be agreed in advance with the supervisory team, and is capped at 5 hours per week.

SECTION D: Resources

17. Resources

Detailed breakdown of project costs:

You should complete the following table for a full-time PhD Studentship conducted over three years. Where a Student is recruited on a part-time basis once awards are made, NISCHR will discuss the financial profiling with you.

Resource	Year 1 £	Year 2 £	Year 3 £	Total £
Directly Incurred				
Consumables	5,800	-	-	5,800
Travel & Subsistence	1,500	1,500	3,000	6,000
Training & Development	80	-	-	80
Equipment	-	-	-	-
Other (please specify)	-	-	-	-
Exceptions*				
Stipend	14,000	14,000	14,000	42,000
Tuition Fees	3,996	4,036	4,076	12,108
Total	25,376	19,536	21,076	65,988
VAT (if applicable)				
Grand Total	25,376	19,536	21,076	65,988

*Please note, as studentships are regarded as an 'exception' under Full Economic Costing (FEC), NISCHR will **not** provide funding under 'directly allocated costs' and 'indirect costs.

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Chorell, E., Moritz, T., Branth, S., Antti, H. and Svensson, M. B. (2009). Predictive metabolomics evaluation of nutrition-modulated metabolic stress responses in human blood serum during the early recovery phase of strenuous physical exercise. *Journal of Proteome Research*, **8**, 2966-77.

Felger, J. C., Li, L., Marvar, P. J., Woolwine, B. J., Harrison, D. G., Raison, C. L. and Miller, A. H. (2013). Tyrosine metabolism during interferon-alpha administration: association with fatigue and CSF dopamine concentrations. *Brain Behavior and Immunity*, **31**,153-60.

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Griffiths, T. L., Phillips, C. J., Davies, S., Burr, M.L., and Campbell, I. A. (2001). Cost effectiveness of an outpatient multidisciplinary pulmonary rehabilitation programme. *Thorax*, **56**, 779–784.

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Kelly, E., Owen, C. A., Pinto-Plata, V. and Celli, B. R. (2013). The role of systemic inflammatory biomarkers to predict mortality in chronic obstructive pulmonary disease. *Expert Review in Respiratory Medicine*, **7**, 57-64.

Kruis AL, Smidt N, Assendelft WJJ, Gussekloo J, Boland MRS, Rutten-van Molken M, Chavannes NH. Integrated disease management interventions for patients with chronic obstructive pulmonary disease (2013). *Cochrane Database of Systematic Reviews*, Art. No.: CD009437. DOI: 10.1002/14651858.CD009437.pub2

Lewis, K. E., Thatcher, L., Hodgson, P., Davies, C. A. and Llewelyn-Jones, C. (2012). Twice versus three-times weekly Pulmonary Rehabilitation in a real-life clinical setting. *Proceeding of the American Thoracic Society*; 351.

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National Institute for Health and Clinical Excellence, NICE. (2011). Management of chronic obstructive pulmonary disease in adults in primary and secondary care. London.

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Sabit, R., Griffiths, T.L., Watkins, A.J., Evans, K., Bolton, C.E., Shale, D.J., Lewis, K.E. (2008). Predictors of poor attendance at an outpatient pulmonary rehabilitation program. *Respiratory Medicine*, **102**, 819-24.

Sansone, S. A., Fan, T., Goodacre, R., Griffin, J. L., Hardy, N. W., Kaddurah-Daouk, R., Kristal, B. S., Lindon, J., Mendes, P., Morrison, N., Nikolau, B., Robertson, D., Sumner, L. W., Taylor, C., van der Werf, M., van Ommen, B. and Fiehn, O. (2007). The metabolomics standards initiative. *Nature Biotechnology*, **25**, 846-8.

Spruit, M.A. Singh, S. J., Garvey, C., et al.: on behalf of the ATS/ERS Task Force on Pulmonary Rehabilitation. (2013). An Official American Thoracic Society/European Respiratory Society Statement: Key Concepts and Advances in Pulmonary Rehabilitation. *American Journal of Respiratory and Critical Care Medicine*, **188**, 13–64.

Wishart, D.S., Knox, C., Guo, A.C. et al. (2009). HMDB: a knowledgebase for the human metabolome. *Nucleic Acids Research*, **37**, 603–610.

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SECTION E: Declarations and CV

18. Declarations

18a) Applicant (PhD Supervisor)[1] declaration:

I declare that I have completed the application form in accordance with the guidance notes and confirm that the information provided is accurate to the best of my knowledge. I declare that I will supervise the academic activities of the applicant should the application be successful.

Signed: 

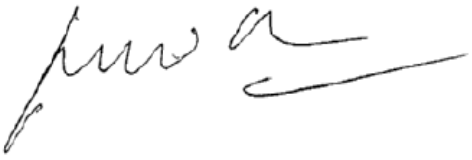
Name: Arwel Wyn Jones

Date: 12/3/2014

Applicant (PhD Supervisor)[1] declaration:

I declare that I have completed the application form in accordance with the guidance notes and confirm that the information provided is accurate to the best of my knowledge. I declare that I will supervise the academic activities of the applicant should the application be successful.

Signed:

Name: Luis Mur 

Date: 12/3/2014

Applicant (PhD Supervisor)[1] declaration:

I declare that I have completed the application form in accordance with the guidance notes and confirm that the information provided is accurate to the best of my knowledge. I declare that I will supervise the academic activities of the applicant should the application be successful.

Signed: 

Name: Keir Lewis

Date: 12/3/2014

18b) Host Institution declaration:

This application should be submitted through the Head of Department and the Administrative Authority, based at the Host Institution, who will be responsible for administering the grant. Both must sign below to confirm that they have read and agreed to the following declaration:

I confirm that I have read this application and that, if this application is successful, the work will be accommodated and administered within this body in accordance with the terms and conditions that will form the contractual obligations. All costs are correct and in accordance with the normal practice of this institution.

	Head of Department	Administrative Authority
Name and initials	Bullen K	Reynolds E
Title	Professor	Mr
Institution	Aberystwyth University	Aberystwyth University
Address	P5, Institute of Human Sciences	Research, Business & Innovation, Visualisation centre
Contact numbers	(01970) 622688	(01970) 622257
Signed	K. Bullen	E. [illegible]
Date	12. 03. 14.	12/3/14

19) Applicant (PhD Supervisor) CV

Personal details

Title: Dr.
Name: Arwel Wyn Jones
Current job held: Postdoctoral researcher

Institution: Aberystwyth University and Hywel Dda University Health Board
Address: F.25, Carwyn James Building, Penglais Campus, SY23 3FD
Phone: (01970) 622282
Email: awj7@aber.ac.uk

Experience

Research experience:

- Investigating the effects of acute exercise on neutrophil function in COPD patients (Postdoctoral)
- Investigating the effects of inhaled corticosteroids and exacerbations on neutrophil function of COPD patients (Postdoctoral)
- Explored the effects of acute and chronic bovine colostrum supplementation and exercise on *in vitro* and *in vivo* immune markers (PhD)
- Explored the effects of chronic bovine colostrum supplementation on oral microbiome, metabolomics and incidence of upper respiratory illness (PhD)

Qualifications:

2010-2013 Aberystwyth University
PhD – 'Effects of bovine colostrum on immune responses following prolonged exercise and upper respiratory illness'

2007-2010 Aberystwyth University
BSc (Hons) Biology & Sports Science
First class degree classification

Work history

2013-Present Postdoctoral researcher and module coordinator for Sport and Exercise Nutrition (Level 3 Undergraduate module) at Department of Sport and Exercise Science, Aberystwyth University)

2010-2013 Teaching assistant and lab demonstrator for Undergraduate students at Department of Sport and Exercise Science, Aberystwyth University

PhD supervision
Co-supervision of PhD student with Prof. Luis Mur and Dr. Keir Lewis from September 2014.

Publications:

Curtis, F., Oliver, E. J., **Jones, A. W**., Rice, S. and Thatcher. (2013). Health and lifestyle changes associated with ageing in rural communities: the emphasis on current concerns in Wales (Welsh Article). *Gwerddon*, 16, 28-39.

Jones, A. W., Cameron, S. J. S., Thatcher, R., Beecroft, M. S., Mur. L. A. J. and Davison, G. (2013). Effects of bovine colostrum supplementation on upper respiratory illness in active males. *Brain Behavior and Immunity*, doi: 10.1016/j.bbi.2013.10.032.

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Personal details

Title: Professor
Name: Luis A. J. Mur
Current job held: Professor at Institute of Biological, Environmental and Rural Science.

Institution: Aberystwyth University
Address: Edward Llywd Building, Penglais Campus, SY23 3DA
Phone: (01970) 622981
Email: lum@aber.ac.uk

Qualifications:
BSc (Hons); PhD

Research experience:
Prof. Mur is a specialist in genomic and post-genomic technologies which are used to investigate pathogenic mechanisms across various biological kingdom: A particular expertise lies in the use of metabolomic approaches involving mass spectrometry using various platforms and data mining based on univariate and multivariate statistics and machine learning (e.g. genetic algorithm). The following are a selection of current projects that are relevant to this proposal:

1) Assessing human pulmonary microbiomic changes in the sputum of COPD and lung cancer patients through next generation sequencing.
2) Metabolomic approaches to identify biomarkers linked to lung cancer in sputum
3) Determining the roles of aspirins and salicylate in the suppression of cancer
4) Describing the effects of extreme environmental stress on the oral microbiome and serum biochemistry. This work forms part of the Sir Randulf Fiennes led “Coldest Journey” Antarctic expedition. http://www.thecoldestjourney.org/
5) Discovering novel antimicrobial metabolites from extremophile bacterial and invasive weeds.
6) Assessing the effect of bovine colostrum on the incidence of upper respiratory illness

PhD Supervision experience:
Since my appointment in 1998 I have supervised over 30 students. Only 1 has failed to submit their thesis with a 4 year deadline. Currently, I am primary supervisor to 4 students and co-supervisor for a further 3 students. I have been frequently been asked to be external PhD examiner for Universities including Manchester, Imperial College, Reading and Edinburgh.

Work history
1991-1997 BBSRC Research Associate, University of Leicester
1997- 2005 Lecturer. Institute of Biological Sciences, University of Wales, Aberystwyth.
2005- 2013 Senior Lecturer, Institute of Biological Science, University of Wales, Aberystwyth /Institute of Biological, Environmental, and Rural Science (IBERS)/ Aberystwyth University
2013- PERSONAL CHAIR

Grants

Welsh Assembly WORD programme (CoI) 2008-10. Early detection of lung cancer: metabolic biomarkers for high risk screening Project No: H07-3-31 E

- BBSRC (CoI): Correlation of metabolic fingerprints with differential growth responses of cold-inhibited salicylate mutants. 1/1/06-31/12/09
- Royal Society: International Project – (PI) The impact of nitric oxide on ethylene signaling. 15/01/08-31/04/10.
- National Science Foundation (CoI) USA: Surveying natural diversity of the model grass Brachypodium distachyon : 2009-2013.
- BBSRC (CoI) 2011-2014 Exploiting Brachypodium distachyon to elucidate drought tolerance mechanisms : Linking gene expression with changes in cell wall chemistry
- Genetic Society 2011 (PI) Microsatelite analysis of genetic diversity in Brachypodium
- BBSRC (PI) Screening for costs of disease resistance caused by stomatal dysfunction: 01/1/11 – 31/12/ 2014
- BBSRC (Co1) Institute Programme Grant; Rumen Systems Biology(2011-2015).

Publications

CLINICAL PAPERS

Jones, A. W., Cameron, S. J., Thatcher, R., Beecroft, M. S., **Mur, L. A**. and Davison**, G.** (2013). Effects of bovine colostrum supplementation on upper respiratory illness in active males. Brain Behav Immun.

Cristescu, S. M., Marchenko, D., Mandon, J., Hebelstrup, K., Griffith, G. W., **Mur, L. A. J**. and Harren, F. J. M. (2012). Spectroscopic monitoring of NO traces in human breath: applications and perspectives. Applied Physics B, 1-9.

Mur, L. A. J. and Ellwood, P**.** (2012). Salicylates and Cancer: Nova.(Book Chapter)

Morgan, G., Rothwell, P., Burn, J., Chan, A**., Mur, L.,** Morton, D., Cuzick, J. and McVie, G**.** (2011). Aspirin, salicylates and cancer: conference. In ecancer, vol. 5.

Lewis, P. D., Lewis, K. E., Ghosal, R., Bayliss, S., Lloyd, A. J., Wills, J., Godfrey, R., Kloer, P. and **Mur, L. A.** (2010). Evaluation of FTIR spectroscopy as a diagnostic tool for lung cancer using sputum. BMC Cancer 10, 640.

Elwood, P. C., Gallagher, A. M., Duthie, G. G., **Mur, L. A. J.** and Morgan, G. (2009). Aspirin, salicylates, and cancer. Lancet 373, 1301-1309.

Mur, L. A. J., Kloer, P., Ghosal, R., Lewis, K. E. and Lewis, P. D**.** (2008). Fourier Transform Infrared Spectroscopy and Metabolic Profiling in Lung Cancer. *Thorax* **63**, A60-A61.

Ghosal, R., Lewis, K. E., Kloer, P., Mehta, R., Parry, D., Llewellyn-Jones, C., Prior, S. L., **Mur, L. A. J.** and Lewis, P. D. (2007). Fourier transform infrared spectroscopy measuring metabolic markers in sputum in patients with and without lung cancer. Thorax 62, A10-A10.

FOOD SECURITY PAPERS

(> 40 PAPERS WITHIN THE LAST REF PERIOD): Examples being:

Kingston-Smith, A. H., Davies, T. E., Rees Stevens, P**. and Mur, L. A. (**2013). Comparative metabolite fingerprinting of the rumen system during colonisation of three forage grass varieties. Plos One 8, e82801.

Lloyd, A. J., William Allwood, J., Winder, C. L., Dunn, W. B., Heald, J. K., Cristescu, S. M., Sivakumaran, A., Harren, F. J., Mulema, J., Denby, K**. Mur. L.A.J** (2011). Metabolomic approaches reveal that cell wall modifications play a major role in ethylene-mediated resistance against *Botrytis cinerea*. Plant J 67, 852-68.

Allwood, J. W., Clarke, A., Goodacre, R. and **Mur, L. A.** (2010). Dual metabolomics: a novel approach to understanding plant-pathogen interactions. Phytochemistry 71, 590-7.

Personal details

Title: Dr.
Name: Keir E. Lewis
Current job held: Associate Professor and Honorary Chest Consultant

Institution: Swansea University and Hywel Dda University Health Board
Contact address: Respiratory Unit, Prince Philip Hospital, SA14 8QF
Phone (01554) 783133
Email: K.e.lewis@swansea.ac.uk

Qualifications:

Undergraduate	
1989-95	United Medical & Dental Schools of Guy's & St Thomas Hospitals
1992	B.Sc. First Class (Hons.) Psychology
1995	MB.BS. (Double Honours)
Postgraduate	
1998	M.R.C.P (U.K.)
2004	MD Thesis, University of Wales, Cardiff.
2010	F.R.C.P (U.K)

Research experience:

After gaining research related degrees (BSc and MD) during medical training, I have progressed through Lectureships, Senior Lectureships and Readership. I have supervised 10 undergraduate / post-graduate students and conceived, designed and funded the Clinical Research Centre in Prince Philip Hospital in Llanelli. This has helped secure 4 major pharmaceutical contracts and boosted our R&D staff from 3 to 12 WTEs and annual budget from £80,000 to £472,000. We have won the MEdiWales Award for Innovation in the NHS and international collaborations with Regensberg, Norway, Galicia, Berlin, Ontario and Kentucky. I have been principal or co-applicant on grants worth over £5M, been R&D Director for Hywel Dda since 2009 and have recently been appointed Dean for Academic Medical Careers, Wales Deanery (2014).

Work history:

2011 – present	Associate Professor in Respiratory Medicine, University of Wales, Swansea and Honorary; Consultant in Respiratory and General Medicine, Hywel Dda Health Board.
2003 -present	Senior Lecturer in Respiratory Medicine, University of Wales, Swansea and Honorary Consultant in Respiratory and General Medicine, Hywel Dda Health Board.
1998 - 2004	Training in Respiratory & General Medicine - Specialist Registrar –various welsh hospitals
1996 - 1998	Royal Hospitals NHS Trust, London, SHO Training Scheme 1996-1998
1995-1996	Pre-registration, Guys & St Thomas's NHS Trust, London

PhD supervision

Currently, I am primary/ co-supervisor to 3 PhD students and 1 MD candidate. I have previously supervised 3 MD candidates to completion and acted as external and internal reviewer for MD theses at Cardiff and Swansea University respectively.

Selected publications:

Lewis AT, Jones K, **Lewis KE**, Jones S, Lewis PD. Detection of Lewis antigen structural change by FTIR spectroscopy. Carbohydr Polym. 2013; 92(2):1294-301.

Ghosal R, **Lewis KE**, Kloer P, Bayliss S, Mur L, Lewis PD. (2010). Fourier Transform InfraRed Spectroscopy on sputum from lung cancer patients, healthy controls and a high risk cohort. Thorax; 65: A19

Ghosal R, **Lewis KE**, Kloer P, Llewellyn-Jones C, Lewis PD. (2007). Fourier transform infrared spectroscopy measuring metabolic markers in sputum in patients with and without lung cancer. Thorax, 62: S19

Lewis KE, Ghosal R, Mur L, Bayliss S, Kloer P, Lewis PD (2011). Using Fourier Transform Infrared (FTIR) on sputum to develop a predictive model to differentiate lung cancer from healthy controls. Proc Am Thoracic Society. A6098

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Roberts SE, Button LA, Hopkin JM, Goldacre MJ, Lyons RA, Rodgers SE, Akbari A, **Lewis KE**. Environmental and socio-demographic factors associated with the incidence and outcome of serious asthma: record linkage study. (2012) Eur Resp J 2012; 40(3):785-8.

Phillips CO, Syed Y, Parthaláin NM, Zwiggelaar R, Claypole TC, **Lewis KE**. Machine learning methods on exhaled volatile organic compounds for distinguishing COPD patients from healthy controls. J Breath Res 2012 ;6 (3):036003

Lewis PD, **Lewis KE**, Ghosal R, Bayliss S, Wills J, Godfrey AR, Kloer P, Mur LAJ. Evaluation of Fourier Transform InfraRed Spectroscopy as a diagnostic tool for lung cancer using sputum. BMC Cancer 2010; 10: 640-6

Lewis KE, Annandale JA, Warm DM, Hurlin C, Lewis L. (2010). Does home telemonitoring further affect quality of life for patients with COPD who have had pulmonary rehabilitation? A pilot randomised trial. J Telemed Telecare, 16: 253-9

Lewis KE, Annandale JA, Warm DM, Blyth H, Syed Y, Hurlin C, Lewis L. (2010). Does home telemonitoring after pulmonary rehabilitation reduce healthcare use in COPD? A pilot randomized trial. COPD; 7:44-50

Annandale J, Hurlin C, **Lewis KE**. Reducing COPD admissions with a specialist chronic disease management team. Nursing Times 2009; 105: 25

Sabit R, Griffiths TL, Watkins AJ, Evans K, Bolton CE, Shale DJ, **Lewis KE**. Predictors of poor attendance at an outpatient pulmonary rehabilitation program. Respir Med 2008; 102 (6):819-24.

Selected grants:

- £563,320 United4Health European Integrated Care Technology Policy Support Programme (Call : CIP-ICT-PSP-2012-6): 2012 European Lead for: Telehealth following hospital discharge for COPD.
- £120,000/£160,000 (NISCHR): 2012-15/2011-2014. To establish NISCHR Clinical Fellows in Hywel Dda Health Board.
- £287,000 Welcome Trust 2011: 'Prognostic factors and outcomes for medical emergency admissions'. Interrogation of a large NHS database.
-£1.5 Million NISCHR: 2011. To develop a Biomedical Unit in Swansea using haemo-rheology to research pro-thromobotic tendency lead.

£420,000 NISCHR: 2011.To strengthen research support infrastructure in Hywel Dda.

-£315,000 Welsh Office for Research and Development (NISCHR). 2010. To establish a Welsh Respiratory Research Network.

-£300,000 Welsh Assembly Government (2009) for telemedicine in chronic disease (Clinical Lead and Chief Investigator).

- £104,000 WORD/NISCHR. 2007. For research into metabolic markers for lung cancer.
- £815,000 Informing Health Care Wales: 2007, European eTEN monies grant C046225 researching telemedicine for COPD (UK Chief Investigator).