

North Wales Organisation for Randomised Trials in Health & Social Care (NWORTH)

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FOREWORD

The North Wales Organisation for Randomised Trials in Health and Social Care, (NORTH), is funded by Welsh Government through Health and Care Research Wales.

This report provides an overview of our work and activity in Year Two of a three year grant from Health and Care Research Wales. Like the report that we wrote for Year One, it demonstrates the range of evaluative methods and approaches that we use as a Clinical Trials Unit (CTU). Equally, it demonstrates our commitment to making a difference to people's health across Wales and beyond.

NORTH was originally founded as a CTU by Professor Ian Russell and his good work was continued by Professor Bob Woods until 2015, cementing NORTH's excellent reputation for testing pragmatic and complex interventions to improve patient care. We now operate a distributed model of leadership at the Unit, under the Directorship of Professor Paul Brocklehurst. In the first two years of funded activity (to May 2017), we have submitted 48 unique grant applications and 16 of these have been awarded (a grant success rate of 33%). Our current portfolio total grant value is £17M, (representing 21 studies), with another £11M currently in submission (8 studies).

In Year Two, NORTH has developed further links with the School of Healthcare Sciences and the Bangor Institute of Health and Medical Research (BIHMR). Professor Brocklehurst is now the Deputy Head of the School (Research) and Operational Lead for the Institute. This opens up new possibilities for research and inter-

disciplinary work at the University. In addition, the Unit continues to build strong collaborations with a wide range of collaborators throughout the United Kingdom (UK). Our Core Operations Group and Project Screening Standard Operating Procedure ensures robust triage and assessment of all collaboration requests and a weekly review of active projects' status allows an agile and timely response to any arising issues.

Year Two has seen good progress made in methodological developments at the Unit. The Statistics team have further improved our randomisation algorithm and we were invited to give two oral and two poster presentations at the International Clinical Trials Methodology Conference in May 2017. We have also been active in a Medical Research Council funded project to evaluate 'Studies Within A Trial'. In addition, we have been successful in obtaining funding to support a part-time PhD student and have won two 'Knowledge Economy Skills & Scholarships' projects; one looking at the potential of Macro 'pop-up' templates in electronic medical records to improve recruitment to clinical trials in primary care; another looking at the value of social networks across Wales. We are also supporting one of our staff to undertake a MPhil and have had a number of trial related papers published this year.

Investment in our staff is critical. We have seen a 78% rise in productivity (when measured by grant capture) during this grant period. All staff performance development reviews are carried out annually and all training is linked back to the Unit's strategy and cascaded to relevant team members. We have invested in training for all of our Unit's functions, with staff attending a variety of internal and external training events. Key progress has also been made in the Welsh translation and linguistic validation of health measures, with 34 linguistically validated Welsh language health measures now available on micym.org.

Perhaps the most important of all of our achievements, is the continuing emphasis that we place on working together. This ensures that the Unit delivers not only for the Welsh Government, but for the people and researchers across Wales.



Professor Paul Brocklehurst
Director of NORTH



INTRODUCTION

What is our mission?

NWORTH is a UK Clinical Research Collaboration (UKCRC) fully registered Clinical Trials Unit (UKCRC CTU Registration Number 23 since 2007), which specialises in the design, conduct, analysis and reporting of Phase II and III RCTs. The Unit is part of the School of Healthcare Sciences and the Bangor Institute of Health and Medical Research (BIHMR).

NWORTH's mission is to improve the health and well being of the people of Wales and beyond by evaluating complex interventions in health and social care. We also seek to advance the theory and practice of randomised controlled trials and other rigorous designs for evaluation.

NWORTH provides a Research Design and Conduct Service to Betsi Cadwaladr University Health Board (BCUHB) and Powys Teaching Health Board. We comprise a

multi-disciplinary and multi-functional team with experience and expertise in healthcare research and clinical studies from initial idea generation through to final publication and dissemination. The Unit collaborates with a broad cross-section of healthcare professionals and clinical academics from across the UK. NWORTH plays a pivotal role in contributing to excellence in health and social care research and development nationally and internationally.

1

Excel as a clinical trials unit undertaking randomised controlled trials, offering seamless processes and service which add value to our collaborators.

2

Increase research activity in areas of strategic and clinical importance (building capability and capacity).

3

Maintain the quality of new trials and studies being adopted onto the Unit's portfolio, ensuring all new enquiries are appropriately and adequately costed and run to time and budget.

4

Nurture and sustain existing collaborations and develop new partnerships and collaborations; linking with local NHS stakeholders and the wider Health and Care Research Wales infrastructure.

5

Provide a Research Design and Conduct Service to encourage and support staff working in Health and Social Care research to develop research proposals.

6

Through LLAIS, facilitate trial participation through the medium of Welsh in order to meet the regulatory and governance requirements of the devolved bilingual context in Wales without compromising scientific rigour.

7

Develop methodological expertise, which is recognised both nationally and internationally.

WHO WE ARE



Core Operational Group Team Members (L-R): Alison Jenkins, Paul Brocklehurst, Ian Woodrow, Jean Ryan, Zoe Hoare.

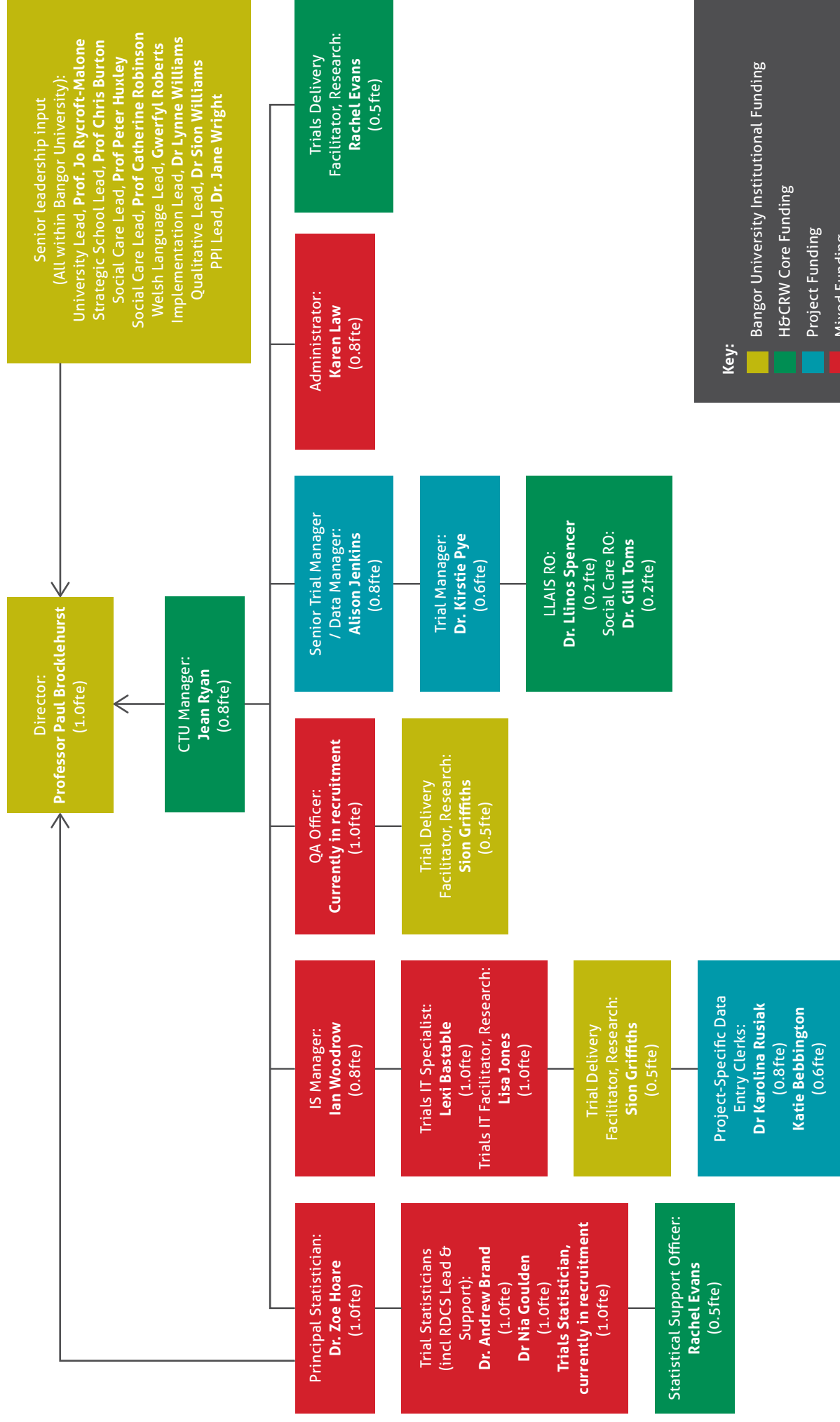
NORTH is divided principally into two functions: trial development and trial delivery. The former is a separately funded component of NORTH and is formally entitled the Research Design and Conduct Service (RDSCS).

Our multidisciplinary team in trial delivery are divided into four main functions: Information Technology, Trial Development and Management, Statistics and Methodology, and Quality Assurance.

Alongside the Director and the Trials Unit Manager, the four Functional Leads form the Unit's Core Operations Group (COG), which meets weekly to provide operational oversight of all studies on NORTH's portfolio. They also assess the quality of incoming collaboration requests and the operational impact of any proposal.

COG's role is crucial in terms of building the Unit's pipeline of projects and proactively anticipating and preparing for changes to legislation and governance requirements.

NWORTH ORGANOGRAM



Key:

- Bangor University Institutional Funding
- H&CRW Core Funding
- Project Funding
- Mixed Funding

WORK PACKAGES:

WP1: Portfolio Development

There has been unprecedented activity and success of the Unit's portfolio during the first two years of the current grant award. From April 2015 to May 2017, 48 unique grant applications have been submitted (where outline to full applications and resubmissions to the same funder have only been counted once), and 16 of these have been awarded, (33%). The total grant value of our current portfolios is £17M, (representing 21 studies), with another £11M currently in submission (8 studies).

WP2: Oversight of Ongoing Studies

With the establishment of the Core Operations Group (COG) and the development of the Project Screening SOP, the triage and assessment of all collaboration requests has become robust. A weekly review of active projects' status allows an agile and timely response to any issues arising. The production and signing off of the Unit's Quality Manual in Year 2 underpins the importance of NWORD's quality related activities and documents the Unit's Quality Policy.

WP3: Building Collaborations

The Unit continues to build collaborations both within the Bangor Institute of Health and Medical Research, (BIHMR) and also with a wide range of collaborators throughout the UK.

We have made links with leading Dental Public Health researchers in the UK and have collaborated with key gerodontologists in Europe. We have also written a position paper for future avenues of research for the European College of Gerodontology. Working with BCUHB, the Quality Assurance Manager at NWORD reviewed six joint SOPs during this period and updated them ready for re-issue. The NWORD Statistics team developed a set of 16 factsheets for BCUHB R&D as an "introduction to statistics and research methodology". These factsheets have been made available to researchers within BCUHB via their intranet and R&D department. This was augmented with a YouTube video: youtu.be/emJYjvpQe0s

NWORD is now linking with key figures in Public Health England and NHS England as part of an evaluation of a practice based dental prevention project in North Yorkshire. This has brought in funding to support a PhD student to undertake a realist evaluation of the programme. NWORD is also working closely with the School of Social Care and has undertaken some provisional mapping work for Professor Fiona Verity.

The Director has also been linking with Professors Torgerson and Bower regarding an on-going methodological work stream at the Unit on Studies Within A Trial (SWATs) (highlighted above).

WP4: Methodological Development

This is an area where we have been very pleased with progress over 2016-2017. The Statistics team has developed methodology around adding continuous stratification variables into our randomisation algorithm, an online tool for exploring recruitment achievability and have conducted a review of published pilot and feasibility studies to understand what domains are considered important and how they are used to inform the subsequent definitive trial.

An internal audit was carried out to establish potential interest in studies within a trial (SWATS) amongst our collaborators. The resulting report was shared with Professor Peter Bower's team as part of an MRC project. Systematic Techniques for Assisting Recruitment to Trials (MRC START) (<http://research.bmh.manchester.ac.uk/mrcstart/about/>) aimed to develop interventions to enhance recruitment into trials, collaborate with on-going research teams to test these interventions in nested studies and rapidly develop the evidence base for recruitment. Building on this collaboration, the team presented their findings at the Society of Clinical Trials in May 2017 with Professor David Torgerson and Professor Shaun Treweek on evidence-based recruitment and retention SWATs.

Further work is on-going using a questionnaire to gain an understanding of attitudes towards SWATs. In addition, a KESS-2 scholarship has been awarded to NWORD entitled "Evaluating the potential of Macro "pop-up" templates in electronic medical records to improve recruitment

to clinical trials in primary care: a Study Within A Trial". The research question being addressed in this application is whether macro "pop-up" templates can improve the recruitment of patients to trials conducted in primary care. We currently have two methodological papers in development on randomisation that will be submitted this year. Another methodological paper is also in development.

WP5: Trial Unit Development

All staff performance development reviews are carried out annually and training needs identified. All training is linked back to the Unit's strategy and cascaded to relevant team members. Training on all core SOPs and job-specific SOPs is completed for all new starters and those requiring updates. Following an internal audit, improvements have been made in the recording of staff training and CPD and how this is followed up.

We have invested in training for all of our Unit's functions in 2016-17, with staff attending a variety of internal and external training events relating to quality assurance, pharmacovigilance, MACRO training and advanced IS training, statistical methodologies, good clinical practice, health and safety management, various Human Resources Management training events and Welsh Language awareness training.

One staff member is being supported to complete her MPhil and is being supervised by the Unit's Director and Principal Statistician.

WP6: Research Design & Conduct Service

The RDCS supports NHS and Social Care professionals to develop high quality research proposals for submission to funding bodies. A concerted effort has been made to link closely with both R&D Departments in Betsi Cadwaladr University Health Board and Powys Teaching Health Board so that services can be tailored to their needs. We have offered a range of workshops, fact-sheets, presentations, drop-in sessions and departmental-specific sessions to highlight the service available. We continue to offer monthly drop-in sessions at sites to ensure the service is available at the point of need.

We have participated in two All-Wales RDCS writing retreats and continue to provide the strategic lead for the RDCS on Social Care and Welsh Language.

WP7: LLAIS

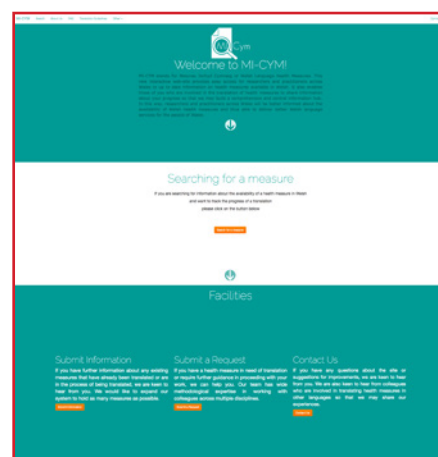
Key progress in this area has been on the Welsh translation and linguistic validation of health measures. This has included the following:

- Nottingham Extended Activities of Daily Living Scale (NEADL)
- EORTC-QLQC30
- EORTC-PR25
- EPIC26
- Decision Regret Scale
- Social Difficulties Inventory
- Patient Support Strategies Questionnaire
- K6

34 names are now on the RHOI LLAIS database of Welsh speaking lay members. In total, NWORDH has offered 148 public involvement opportunities during 2015-2017.

An evaluation of the ELAN standards was completed at NWORDH with an action plan produced. Training on Welsh language awareness was provided for all NWORDH staff. Both the LLAIS website and Micym websites have been updated. Details of all measures are available at www.micym.org.

Gwerfyl Roberts won an award from Queen's University, Belfast to undertake the Welsh translation and linguistic validation of the Life After Prostate Cancer Diagnosis Survey which has now been completed.



CROSS-CUTTING THEMES:

PPI

PPI has been embedded into all NWOORTH applications during this period. Close links have been made with Age (Cymru), Healthcare Forum (Wales), the lay appointed member of the Wales Ministerial Advisory Board on Ageing, the National Partnership Forum for Older People and with the Lead for Health and Education. The Director works closely with the Citizen Scientist project (<http://www.citizenscientist.org.uk/research-opportunities/dental-research/oral-health-for-older-people-who-are-cared-for-at-home/>).

These links have been used to develop a Priority Setting Partnership for older people to ensure all older people have a voice in setting the research agenda for dental service provision (<http://www.citizenscientist.org.uk/research-opportunities/dental-research/setting-priorities-for-the-dental-care-of-older-people/>). This led to a Discrete Choice Experiment to examine the preferences of older people for oral health services. This was undertaken in Manchester, Salford, North Wales and Cork and was presented at the International Association of Dental Research in 2017. A paper has also been submitted to BMC Oral Health on using inductive approaches to involving older patients in directing the research agenda "How do we incorporate patient views into the design of health-care services for older people". PPI was also an important element of a recently published paper by the Director and researchers with links to NWOORTH entitled "Implementation and trial evidence: a plea for forethought" (Br Dent J 2017;22(5):331-335). It also formed a substantive element of recent presentations to researchers in Cork (Health Research Board in January 2017) and Belfast (Centre

for Public Health in March 2017) on "How to account for context in clinical trials" and the Invited Session at the Society of Clinical Trials in May 2017 "How to design implementation into your trial from the outset".

PPI has been utilised in one of our active studies. RHiNO: Respiratory Health In Preterm Neonatal Outcomes, (Kotecha, S. et al, Cardiff University, MRC), where a parents panel was convened and researchers conducted face-to-face meetings with 12 sets of parents with preterm-born children seeking their views on the concepts, design and feasibility of the research proposal. The nominated patient representative provides parental input and children's views after regular meetings with the wider consumer group. The group has reviewed all relevant written information prior to governance approvals. A website (<http://rhino-health.org>) with regular newsletters is produced with the lead on content coming from the patient representative.



Social Care

NWORTH takes the strategic lead for social care as part of the All-Wales RDCS. As such, a number of meetings have been held with Professor Fiona Verity to discuss the remit of the School and how it will complement the role of the RDCS.

The new School will work in three areas to:

1. Encourage, promote and facilitate a social care research programme around four themes: (i) social determinants of care needs, (ii) prevention and early intervention, (iii) social care delivery and, (iv) institutional structures and policies.
2. Collaborate with Social Care Wales and Health and Care Research Wales Support Centre and existing social care research providers to support research capacity building in social care to strengthen the research and the capabilities of people who do research.
3. Support research knowledge mobilisation and public engagement in social care research in collaboration with the above organisations.

One of the aims of the School is to lead and promote the development of a culture of research mindedness, evidence-enriched practice and research activity in social care services in Wales. It is envisaged that the School will assist practitioners at the early stages of the research process as currently the culture of conducting research is currently not at the RDCS level for practitioners. NWORTH will continue to link closely to ensure that it provides the strategic link to the School and that support for social care continues to be offered via the RDCS.

Commercial Partners

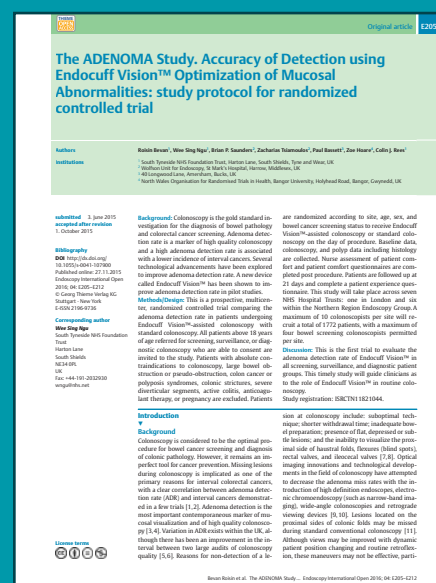
Two studies on the portfolio during this period have been industry funded - ADENOMA, (completed October 2016) and B-ADENOMA, (currently recruiting), both Rees, C. (South Tyneside NHS Foundation Trust). Funding has been provided by ARC Medical Design Ltd. who developed the Endocuff Vision™ to improve adenoma detection rates in colonoscopies. They provided funding to test adenoma detection rates in a randomised controlled trial led by Professor Colin Rees. Following the success of the ADENOMA collaboration, (the trial demonstrated a significant improvement in adenoma detection rate with no serious adverse effects - results in press), ARC Medical are currently funding the B-ADENOMA study, which is being conducted in subjects referred and scheduled for screening flexible sigmoidoscopy via the NHS English Bowel Scope Screening Programme and will compare Endocuff Vision®-Assisted Flexible Sigmoidoscopy with Standard Flexible Sigmoidoscopy.

As the study is being conducted on existing NHS Bowel Cancer Screening Programme lists, there is no extra cost to the NHS. Funding is provided by ARC Medical Design Ltd to cover the Endocuff Vision™ devices, CTU costs, results analysis and dissemination. Any unforeseen costs related to the study will be met by ARC Medical Design Ltd.

This collaboration provides a good example of how initial industry collaboration with research conducted at 7 sites has led to a much larger study, which is now being conducted at 18 sites across the UK.

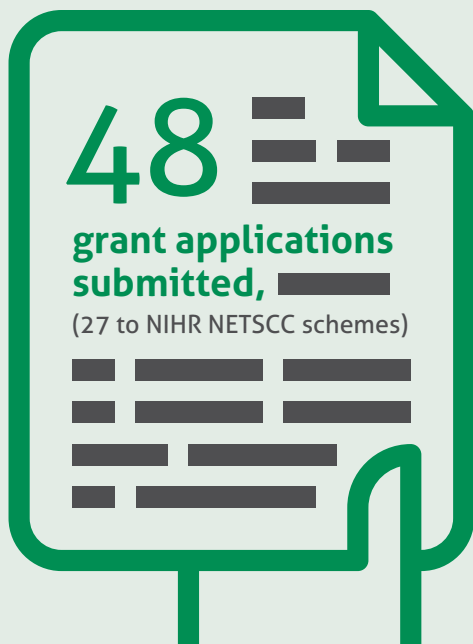
Another example of an industry-funded collaboration is our work on the HG Trial, (Management of Pelvic Girdle Pain in Pregnancy using

Harness Gravidarum: A Randomised Controlled Trial comparing current treatment with a new device). Funding for this study has been provided jointly by HGR Ltd., (who manufacture the pelvic girdle) and BCUHB. The research was recently awarded the Judges Award at the MediWales Research and Innovations award ceremony in December 2016.



KEY ACHIEVEMENTS

Some key metrics of our performance for 2015-2017:



We have more than doubled the average yearly income coming into the Unit from project funds, (£400k on average in the previous round; **£1M** on average during this grant period).

Key Performance Metrics developed inductively within the Unit are **all green**

CASE STUDY GREAT TRIAL

NWORTH collaborated on the GREAT trial from inception to completion.

The research findings have shown that personalised cognitive rehabilitation therapy can help people with early stage dementia to significantly improve their ability to engage in important everyday activities and tasks.

The large-scale trial found that cognitive rehabilitation leads to people progressing in areas that enable them to maintain their functioning and independence.

The Goal-oriented Cognitive Rehabilitation in Early-stage Alzheimer's and Related Dementias: Multi-centre Single-blind Randomised Controlled Trial (GREAT) trial involved 475 people across eight sites in England and Wales.

The researchers found that those who took part in the therapy showed significant improvement in the areas they had identified. The goals participants chose were varied, as dementia affects people in a wide range of ways. Some wanted to manage daily tasks better; for example a participant from North Wales, featured on the BBC's Horizon programme in May 2016, worked with a therapist to develop strategies to prevent him burning food when cooking meals.

Professor Linda Clare, of the University of Exeter and formerly of Bangor University, who led the research, said:

“We now know that cognitive rehabilitation effectively supports people to achieve the everyday goals that matter to them. The next step is to quantify benefits such as whether this approach delays the need for people to go into care homes by supporting them to live independently for longer. This could have important financial benefits for social care. We must also assess whether the therapy can be integrated into how practitioners routinely work, so that more people can have access and are supported to live better lives with dementia.”

NWORTH was involved in designing the study methodology; they designed and carried out its statistical analysis, developed, tested, deployed and maintained the study's electronic data capture systems and provided quality assurance input for all aspects of the sizable, multi-centred trial.

Dr Andrew Brand, Trial Statistician for the study commented

“It was great to work with such an experienced trial team and to be involved in research tackling dementia, which is such a prevalent and debilitating condition. We congratulate the team on their significant achievement.”

Prof Bob Woods of the University's Dementia Services Development Centre, led the research from Bangor University and said:

“Having been involved in developing this approach over a number of years it is exciting to see the evidence for its benefits becoming clearer. We are grateful to all the participants and families for giving readily of their time, and to our colleagues at Betsi Cadwaladr University Health Board, who made it possible for North Wales to be the top-recruiting site. We now plan to continue working closely with them in making the approach widely available in the years to come.”

Dr Ola Kudlicka, who managed the trial, said:

“We know there's a great deal that can be done to support people to live well with dementia. Our research is about finding out what matters most to individuals and working with them to find strategies to manage important tasks and maintain their interests. Contrary to popular belief, our trial shows that people with early-stage dementia, given the right kind of support, have the capacity to learn and to improve their skills. We aim to support them in their right to live a fulfilling and happy life and be as independent as possible.”

NWORTH is currently involved with the GREAT research team on another submission.



LOOKING AHEAD

Our prime aim going forward is to continue our current success in growing the portfolio, (where we are currently exceeding our performance target).

We aim to increase our return on investment for every pound invested by Health and Care Research Wales.

We will continue to foster links with key researchers across the UK and concomitantly seek to increase the number of Bangor-led grants via BIHMR in order to maximise our research output and impact (building on our performance in REF 2014). Our portfolio now reflects a much broader range of collaborations, research themes and clinical theme areas whilst also targeting NETSCC funding and winning much larger research grants.

We will also actively build on our existing partnerships to further our collaborations and strategic links with Besti Cadwaladr University Health Board.

We will continue to work closely with a broad range of PPI groups to ensure that PPI is embedded within all of our applications.

Linking with Professor Verity and Dr Gill Toms we will develop a robust plan for improving the infrastructure for social care research based on the mapping exercise already undertaken. We aim to develop a culture of research mindedness, evidence-enriched practice and research activity in social care services in Wales.

We will continue to develop four methodological work-streams (WSs), which we started in this current funding period.

1

Feasibility / pilot

In this WS, NWORTH is exploring how pilot and feasibility studies are being used and the types of information that inform definitive trials. Initial work has already mapped the number and type of studies being conducted across the UK and was presented at the Society of Clinical Trials in Liverpool in 2017.

2

Randomisation

The aim of this WS is to extend the dynamic adaptive randomisation algorithm developed at NWORD to be able to accept continuous stratification variables, such as age. This will reduce imbalance across stratification variables and improve the sensitivity of stratification schemes, which is an important consideration when randomising patients into different groups. This work was presented at the Society of Clinical Trials in Liverpool in 2017.

3

Studies Within A Trial (SWATS)

This WS builds on the work already undertaken with Professors Torgeson, Bower and Treweek. Professor Brocklehurst and Ms Evans from NWORD presented the on-going work to an international audience in an Invited Session at the Society of Clinical Trials in Liverpool in 2017. In addition, NWORD has also recently been awarded another KESS-2 scholarship fund to support an MPhil entitled "Evaluating the potential of Macro "pop-up" templates in electronic medical records to improve recruitment to clinical trials in primary care".

4

Implementation

Building on papers published in 2017 and another invited session at the Society of Clinical Trials, the Unit is working with Implement@BANGOR (another research group within BIHMR) to explore the potential of implementation research in the design and conduct of clinical trials of complex interventions.

The Unit also remains committed to exploring research opportunities through the medium of the Welsh language and leading the Health & Care Research Wales infrastructure. We will continue to support on-going research and clinical communities across Wales through active web-site www.llais.org and validation of Welsh language versions of health outcome measures, enabling assessment according to language needs, without compromising data validity www.micym.org.

CONCLUSIONS

The productivity of NWORTH has increased by 78% over the last two years, reflecting the real progress the Unit has made in re-structuring and streamlining resources.

We have also seen some real progress in our metrics and outputs, with approaching three-quarters of all fully costed applications proceeding to a full stage application and a third being funded.

We have maintained good links with research teams across the UK and have engaged in studies in clinical areas ranging from dementia, cancer, neonatal health, oral health and an intervention for adult male offenders.

There are exciting times ahead with NWORTH drawing on the strength of the new Institute within the University (Bangor Institute of Health and Medical Research) to sustain and grow research excellence and conduct research of the highest standard with UK and international impact. As outlined in the introduction, the Unit has now put in place many changes which have put it on a solid footing to deliver and exceed on its objectives. Year Three will represent an opportunity to build on these strengths and push for further growth.



Professor Paul Brocklehurst
Director of NWORTH CTU



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