Health in the West Midlands: The Hill Study

Study Protocol

This protocol has regard for the HRA guidance

Version 1.1~~0~~, dated 2~~8~~8-~~Sept~~Nov-2017

Sponsor code: RG-0255-17

IRAS No. 233714

SIGNATURE PAGE

The undersigned confirm that the following protocol has been agreed and accepted and that the Chief Investigator agrees to conduct the trial in compliance with the approved protocol, GCP guidelines, the Sponsor's SOPs, and other regulatory requirements as amended.

I agree to ensure that the confidential information contained in this document will not be used for any other purpose other than the evaluation or conduct of the study without the prior written consent of the Sponsor

I also confirm that I will make the findings of the study publically available through publication or other dissemination tools without any unnecessary delay and that an honest accurate and transparent account of the study will be given; and that any discrepancies from the study as planned in this protocol will be explained.

For and on behalf of the Study Sponsor:

Signature: Date:

..../...../.....

Name (please print):

.....

Position:

.....

Chief Investigator:

Signature: Date:

..../...../.....

Name (please print):

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LIST OF ABBREVIATIONS

CI	Chief Investigator
DMC	Data Monitoring Committee
GCP	Good Clinical Practice
ICF	Informed Consent Form
DMC	Independent Data Monitoring Committee
PI	Principal Investigator
PIS	Participant Information Sheet
QA	Quality Assurance
QC	Quality Control
REC	Research Ethics Committee
SMF	Study Master File
SMG	Study Management Group
SOP	Standard Operating Procedure
TMG	Trial Management Group
TMF*	Trial Master File

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KEY STUDY CONTACTS

Chief/ Principal Investigator	Dr Ross Wilkie, Senior Lecturer in Public Health & Epidemiology, Arthritis Research UK Primary Care Centre, Research Institute for Primary Care & Health Sciences, Keele University, Keele, Staffordshire, ST5 5BG. Tel: 01782 734845; Email: r.wilkie@keele.ac.uk; Fax: 01782 733911
Co-Investigators	Prof George Peat, Professor of Clinical Epidemiology, Arthritis Research UK Primary Care Centre, Research Institute for Primary Care & Health Sciences, Keele University, Keele, Staffordshire, ST5 5BG. Tel: 01782 733906 (734707); Email: g.m.peat@keele.ac.uk; Fax: 01782 733911 Prof Kelvin Jordan, Professor of Biostatistics, Arthritis Research UK Primary Care Centre, Research Institute for Primary Care & Health Sciences, Keele University, Keele, Staffordshire, ST5 5BG. Tel: 01782 733924; Email: k.p.jordan@keele.ac.uk; Fax: 01782 733911 Dr Dahai Yu, Research Associate: Chronic Disease Surveillance, , Arthritis Research UK Primary Care Centre, Research Institute for Primary Care & Health Sciences, Keele University, Keele, Staffordshire, ST5 5BG. Tel: 01782 734891; Email: d.yu@keele.ac.uk Fax: 01782 733911
Statistician	Prof Kelvin Jordan, Professor of Biostatistics, Arthritis Research UK Primary Care Centre, Research Institute for Primary Care & Health Sciences, Keele University, Keele, Staffordshire, ST5 5BG. Tel: 01782 733924; Email: k.p.jordan@keele.ac.uk; Fax: 01782 733911
Sponsor	Keele University, Staffordshire, ST5 5BG.
Sponsor Representative	Dr Clark Crawford, Head of Research Integrity, Directorate of Research Innovation and Engagement, IC2, Keele University, ST5 5NH Tel: 01782 733371; Email: research.governance@keele.ac.uk
Clinical Trials Unit	Keele CTU, Keele University, Keele, Staffordshire, ST5 5BG. Email: ctu.operations@keele.ac.uk

STUDY SUMMARY

Study Title	Health in the West Midlands	
Internal Ref. Number (or short title)	The Hill Study	
Study Design	Cross-sectional survey	
Trial Intervention (where applicable)	N/A	
Study Participants	● Adults aged 35 years and over ● Continuously registered at the practice for a minimum of 10 years prior to survey	
Planned Sample Size	Approx. 27,000, mailed out in 4 batches of 6-7,000, using approx. 8 or more GP practices across West Midlands CRN	
Treatment duration	N/A	
Follow up duration	N/A	
Planned Study Period	November 2017 until end of October 2019	
	Objectives	Outcome Measures
Primary	What are the most common and disabling patterns of long-term condition multimorbidity in the local population and how are such individuals currently being managed? Which long-term conditions, health outcomes and risk factors are most strongly patterned by socioeconomic status (education, occupation, and income), how evident are these social gradients in young, middle, and late adulthood, and are social gradients most evident in multimorbidity and more severe disease? What is the extent of the impact of long term health conditions on healthy working life expectancy and the number of years of life with disability in the West Midlands, and how does this differ by occupation?	Disability and the impact of health conditions were measured in the questionnaire using EQ-5D[28] single items to measure pain frequency and intensity[29], Hospital Anxiety and Depression scale[30], Jenkins Sleep questionnaire, Promis Physical limitation short form[32] and the Promis ability to participate short form[32] . Work loss and productivity will be measured using the Work productivity and Activity Impairment Scale as confounders.

Secondary	Does low health literacy contribute to polypharmacy and adverse outcomes? Does baseline cardiovascular risk influence the provision of evidence-based therapy and what are the complications associated with the provision of such therapy? How does comorbid chronic pain modify the outcomes and management of other non-musculoskeletal long-term conditions? What is the added contribution of undiagnosed comorbid depression to morbidity and disability in the West Midlands? What is the current rate of smoking behaviour (nicotine replacement, smoking reduction or cessation) in the West Midlands?	In addition to the instruments described above the questionnaire also contains instruments to measure tobacco and alcohol use, physical activity, height and weight, caregiving duties, social networks and support, resilience, cognitive ability, health literacy and cardiovascular risk.

ABSTRACT

The prevention and management of chronic non-communicable disease represents one of the greatest challenges facing the economy and healthcare systems of the West Midlands. Primary care has a critical role in the response to this challenge and information from this setting is increasingly recognised as a driver and resource for public health policy, clinical practice, and research. In 8 or more general practices we will undertake a cross-sectional postal survey of up to 27,000 adults aged over 35 years, with linkage (among consenting survey respondents) to high-quality primary care electronic health records further patients may be contacted if response rates are lower than expected. Cross-sectional analyses will determine the occurrence, impact, and healthcare outcomes of adults with selected major long-term conditions, with particular focus on multimorbidity, disability, and work. We will examine the extent of health inequalities in these and in the key social and behavioural risk factors that are believed to determine them. A series of 'Spotlight Studies' will offer local doctors in training a range of supervised research projects, based on local health data, in key areas of importance and supervisory expertise. Our study will also produce long-term legacies through the creation of a world-class source of data for health research on long-term conditions across the adult lifespan.

1. BACKGROUND & RATIONALE

Improvements in years lived with disability are failing to keep pace with increases in life expectancy[1] and it is common chronic non-communicable diseases that are the major contributors to this trend in population health.[2,3] These include musculoskeletal disorders, mental illness and behavioural disorders, chronic respiratory disorders, and cardiovascular diseases, which together account for 50-70% of all years lived with disability from the age of 25 years in the UK.[4] There is an urgent need to provide more effective and efficient means of maximising quality of life and minimising harm for the growing numbers of people with multimorbidity (two or more co-occurring conditions[5]) but also to strengthen the prevention of these conditions, and build more public health activities into the healthcare system.[6-8]

Epidemiological research provides essential evidence to inform health and social care policymakers and professionals, as well as patients and the public, with increasing emphasis on applied outcomes-based research across the lifecourse, team science (including patient/public involvement and engagement), and intelligent use of 'big data'.[9,10] In North Staffordshire, we have a unique longstanding academic-clinical collaboration on epidemiologic research focussed on primary care electronic health record data. The Medical Institute's Industrial & Community Health Research Centre was a founding partner and key driver of the initiative that led to the creation of the Consultations in Primary Care Archive (CiPCA). This is an electronic health record database containing anonymised routinely recorded, regularly audited, high-quality information[11-13] including reasons for consultation, prescriptions, sickness certification, referrals and tests from general practices in Staffordshire Moorlands, Stoke-on-Trent, and Newcastle-under-Lyme dating back to the year 2000. Existing ethical approval allows us to download the anonymised medical record information from these general practices for research use. Peer-reviewed publications using CiPCA include reporting of prevalence and incidence of morbidity presented to primary care,[14-16] distinct developmental trajectories of multimorbidity in older adults,[17] patterns and appropriateness of primary care management,[18-20] and investigation of presented symptoms related to future onset of morbidity.[21-23] Local doctors have been involved in all of these projects, and these data have supported several medical student projects at undergraduate and postgraduate levels.

Primary care electronic health records allow important insight into long term occurrence, management and outcomes across clinical conditions. Its limitation is lack of additional patient-reported information: specifically patient-reported outcomes and information on social and behavioural risk factors.[24,25] Without this linked information our understanding of the impact of health conditions, outcomes of healthcare, and the multiple determinants of these is limited.
Our proposal intends to link self-reported information from a cross-sectional survey of adults across the West Midlands to (with consent) high quality medical record information from general practices with proven quality of recording. Using this resource we will assess the prevalence of social and behavioural risk factors for poor health and outcomes, and determine inequalities in health and barriers to health care use within the West Midlands. Aside from these core questions which cut across all morbidity, we will address a number of more specific "spotlight" questions. The linked database will become a valuable resource for nested projects including those undertaken by undergraduate and postgraduate medical students.

1.1 Aims and objectives

The aim of this study is to provide new evidence and insights that will underpin and inform the prevention and management of chronic non-communicable diseases that cause the greatest burden in years lived with disability in West Midlands. Through a large-scale cross-sectional survey of key patient-reported outcomes and 'psychosocial vital signs' of the adult population and with linkage to high-quality electronic health record data among consenting respondents, our proposal will provide a detailed description of health, key comorbidity and care among consulters in one geographical area. The survey will address the following **primary research questions**:

1. What are the most common and disabling patterns of long-term condition multimorbidity in the local population and how are such individuals currently being managed?
2. Which long-term conditions, health outcomes and risk factors are most strongly patterned by socioeconomic status (education, occupation, and income), how evident are these social gradients in young, middle, and late adulthood, and are social gradients most evident in multimorbidity and more severe disease?
3. What is the extent of the impact of long term health conditions on healthy working life expectancy and the number of years of life with disability in the West Midlands, and how does this differ by occupation?

The **secondary research questions**, to be addressed through a series of *Spotlight Studies* targeted at evidence gaps of high priority to the health of the local population and aligned to specific areas of expertise among local researchers, include:

4. Does low health literacy contribute to polypharmacy and adverse outcomes?
5. Does baseline cardiovascular risk influence the provision of evidence-based therapy and what are the complications associated with the provision of such therapy?
6. How does comorbid chronic pain modify the outcomes and management of other non-musculoskeletal long-term conditions?
7. What is the added contribution of undiagnosed comorbid depression to morbidity and disability in the West Midlands?
8. What is the current rate of smoking behaviour (nicotine replacement, smoking reduction or cessation) in the West Midlands?

This project will provide the following **long-term legacies**:

- Creation within the West Midlands of a unique world-class source of data for health research on long-term conditions across the adult lifespan with linkage of core, validated patient-reported outcomes, social and behavioural determinants to high-quality anonymised electronic primary care data, and use of this as a focal point for local medical research collaborations.
- Provision of a series of practical hands-on research projects based on anonymised health information from the people of the West Midlands to Keele University medical undergraduate and postgraduate students, spanning short summer studentships to doctoral research projects.
- The commitment from research team to identify funding for a repeat survey 5 years after the baseline survey thereby enabling long-term evaluation of changes in patient-reported health and key social and behavioural determinants

2. PLAN OF INVESTIGATION

Overview

We propose to conduct a cross-sectional survey of key patient-reported outcomes and 'psychosocial vital signs' at baseline in a random sample of adults aged 35 years and over registered with 8 or more practices in the West Midlands that have electronic health record data since 2000. We will link the survey data to the primary care electronic health records for those who provide written consent. The electronic health record data will be anonymised, routinely recorded, regularly audited, high-quality information including reasons or consultation prescriptions, sickness certification, referrals, investigations and neighbourhood deprivation dating back to the year 2000 and for 12 months following baseline.

Project timeline

0-6 months (Oct 2017-Mar 2018): Design and test management and data entry databases survey.

6-24 months (Apr 2018-Oct 2019): Data entry, cleaning, linkage to medical records, data analysis and dissemination

2.1 Materials and methods

Design:

Cross-sectional survey (pen-and-paper) with responses linked (with patient consent) to primary care electronic health records.

Participants:

The survey will be sent to a random sample of registered adults aged 35 years and over, drawn from a clinical system search of 8 or more general practices in the West Midlands. Further patients may be contacted if response rates are lower than expected. Patients who meet exclusion criteria will not be included in the study (please see below).

Eligibility criteria:

Inclusion criteria:

- Adults aged 35 years and over
- Continuously registered at the practice for a minimum of 10 years prior to survey

Exclusion criteria:

- Unsuitable for survey due to severe illness, severe learning difficulties, recent diagnosis of terminal illness, major psychological disorder
- Previously stated they do not wish their medical record data to be used for research
- Unable to read/understand English

Notification of general practices:

8 or more general practices (selected to ensure geographical and socio-economic representation of the West Midlands) will be invited to participate in writing, via email and/or practice visits. Each participating practice will be sent a letter summarising the project together with a practice pack containing a copy of the study protocol, letters of approval, and study documentation. GP practice consent to participate will be formalised through HRA standard agreements.

***Pre-testing and piloting*:**

We will adopt a number of strategies in the design stage suggested to help minimise the threats to validity of the general national trend in declining response rates and selective nonresponse. In the invitation letter we offer a telephone number for questions about the survey. The survey questionnaire and administration have already been tested in pre-testing and from our experience from other studies.

Pre-testing: Members of our centre's Patient and Public Involvement and Engagement Research Users Group (RUG) have reviewed the survey questionnaire. The members of the RUG group found the survey questionnaire as a whole and individual items to be acceptable. No items were identified as being sensitive or would cause excessive distress.

The survey methodology has been informed and tested in previous studies undertaken by the centre. We are following the same administration procedures for other cross-sectional studies undertaken by the centre in the last 12 months to samples of 9,000 and 16,000. A number of instruments in the survey instrument for this study have been included in previous studies and levels of missing data have been minimal (i.e. less than 5%). Administration has been successful for both of these surveys.

Data collection:

The survey will be completed using pen-and-paper. We will use a two-stage mailing procedure:

Stage 1: Patients will be sent a Study Pack including a Survey and Participant Information Sheet together with an Invitation Letter from their General Practice inviting them to take part in the study and a prepaid envelope to return the survey. All patients will be given the contact telephone number of the research team who will give any other information about the project if needed.

Stage 2: Non-responders will be sent another Study Pack after 3 weeks (contents as above).

Participants will also be asked to provide written informed consent (i) for linkage of their responses to their primary care medical record and (ii) to be contacted to participate in future studies.

Non responders after 6 weeks will be assumed to have declined participation and will not be contacted again. Patients who indicate they do not wish to take part in the study in the initial recruitment stage will have this recorded in the database and will not receive any follow-up mailings.

Return of completed surveys will be taken as implicit consent for the use of the survey data they provide. Written consent for (i) linkage of their responses to their primary care medical record; and (ii) to be contacted to take part in additional studies will be provided by signing and entering their name and address on a detachable consent form on the final page of survey.

Survey content:

Survey Instrument The content of the survey instrument will contain validated measures:

- general health status (EQ-5D[28]) and subjective health states - pain frequency and intensity,[29] anxiety and depression symptoms (HADS[30]), sleep quality,[31] social participation.[32]
- core demographic, psychosocial and behavioural factors: age, gender, employment status, marital status, educational attainment, occupational class, perceived adequacy of income, area-level deprivation score from postcode[33], tobacco and alcohol use, physical activity, height and weight, caregiving duties, social networks and support, resilience,[34] cognitive ability.

It will also include specific instruments and items for the secondary questions (Spotlight Studies):

- brief measure of health literacy[35]; items required for calculating cardiovascular risk scores[36,37].

Medical record linkage For respondents consenting to linkage, we will link survey information to their primary care medical records within a standalone study database, using a unique study ID as the identifier. Records will initially be collated from first registration or year 2000 (whichever is earliest) to one year after survey response, with subsequent collation for 12 months post survey.
Consultations for morbidities will be identified in consenters' medical records using Read morbidity codes. We have already derived, through GP consensus, code lists for common cardiovascular[39], musculoskeletal,[13,15,18] mental health,[40] and respiratory[40] conditions. We will adapt other publicly accessible codelists[41] or use similar GP consensus approaches to identifying morbidities from the medical records for which we do not have code lists. Similar approaches will be used to identify other information from the records (e.g. prescriptions[19,42] and sickness certification[43]).

If a participant withdraws consent for linkage, then no further information will be gathered. However, data gathered up to the point of withdrawal will be included in the study analyses, unless the participant explicitly states that they do not wish this to happen.

Sample size The total registered population aged ≥35 years to be sent the survey from the 8 or more practices is up to 27,000. An expected combined survey response and consent to linkage of 33% would give 9,000 participants. This will allow us, for example, to determine the overall prevalence of a health condition or multimorbidity with a margin of error of less than 100 per 10,000 (at the 95% confidence level) for any level of prevalence. It is also sufficient to compare between socio-economic groups. For example, a sample size of 9000 will allow us to determine an odds ratio of 1.25 or greater between least and most deprived groups (80% power, 5% significance level), when participants are placed into 5 equal deprivation groups. If response rates are lower than expected, further patients may be contacted.

2.2 Data entry, cleaning, storage

Data entry. Each participant will have a unique study ID. The survey will be designed in TeleForm which will allow data to be scanned into a database specifically designed for this study. Prior to data entry, this database will be tested using a set of dummy data.

Logging of response and consent in the study database will be performed by the Study Administrator. Personal data received on the consent form will be held separately from the data entry databases. The data is to be housed within the Keele Clinical Trials Unit (CTU) secure virtual network, which requires two factor authentication in order to access it. The network also holds a level 1 in the government backed scheme, Cyber Essentials. Roles and permissions within the database prevent unauthorised user access. Prior to data cleaning, the Teleform data will be held on a Keele University server with controlled access. All databases will conform to current data protection laws.

Data cleaning. All scanned data, from the survey, is machine read within the TeleForm software and any anomalies detected by the software require real-time manual verification. All verified data is then cleaned, under the supervision of the study statistician.

Data storage. Surveys will be pseudonymously stored by Research Institute of Primary Care and Health Sciences for a minimum of 5 years in line with Keele CTU standard operating procedures. Completed consent forms will be securely stored separate to research data. All trial databases and participant information are housed in the CTU Secure Network, which is a secure virtual network requiring Two Factor Authentication in order to access the data stored within there.

2.3 Patient and Public Involvement and Engagement (PPIE)

PPIE occurs in this application at all levels, from design (Research Users Group), through to delivery and dissemination, helping to ensure the relevance of the study to patients, researchers, health service planners and practitioners. Our experienced primary care Research Users Group (RUG), formed in 2006, has 75 RUG members in over 67 projects in all stages of research and covering a wide range of musculoskeletal conditions. Our Arthritis Research UK Primary Care Centre-of-Excellence grants provide funding to underpin infrastructure costs of our PPIE activity in research. RUG members are supported by a PPI Coordinator and Support Worker.

Our RUG has had a significant effect on increasing the impact of our research output in a way that supports rapid translation and implementation. The Research Institute is committed to involving patients and the public in its research, using the INVOLVE framework as the starting point for how we structure and implement PPIE. For this proposed body of research we have actively listened to users' experiences of primary health care for chronic health conditions through qualitative interviews in previous studies and RUG meetings. We have convened two dedicated workshops with RUG members - including patients with chronic long term conditions - to identify their perspectives on the use of linked anonymised data for this research. They also strongly felt that publishing accurate information on trends and variation in chronic conditions, their management and outcome would have tangible patient benefit. Use of this information would be maximised by engaging those who could act on the information. These comments and suggestions have fed directly into the proposed project.

As described above members of the RUG group have been involved in the development of patient information and pre-testing of the questionnaire.

2.4 Analysis

Analyses will use self-reported patient measures linked to health care data through the study database. We will use appropriate generalised linear mixed models in analyses to account for clustering of patients in practices. Response rates and sample disposition will be reported in accordance with recommended standards.[44,45] Selective non-response (based on age, gender and deprivation score) will be evaluated and adjusted for using established approaches,[46-48] and techniques applied in our previous studies.[49]

1) *Patterns and management of multimorbidity*. We will base multimorbidity on co-existing self-reported symptoms and on primary care recorded information. We will compare, in a nested methodological study, statistical approaches such as latent class and cluster analysis[17,50] to identify common patterns and trajectories of multimorbidity, as well as simpler approaches such as counts of morbidity. We will then use appropriate models (e.g. multinomial logistic regression) to compare across patterns of multimorbidity on area deprivation, health status, core demographic, psychosocial and behavioural risk factors, and health literacy. Within those with multimorbidity, we will determine extent of polypharmacy (number of prescribed medications) and assess how this varies by area deprivation, the risk factors and health literacy, controlling for multimorbidity, using Poisson or negative binomial regression models as appropriate.
2) *Extent of health inequalities for long term conditions and risk factors.* We will determine prevalence of long term-conditions presenting to primary care, including musculoskeletal, cardiovascular, mental health and respiratory and compare to prevalence figures obtained from other databases. The prevalence of the self-reported core demographic, social and behavioural risk factors will be estimated in survey respondents with weighting applied to account for selective non-response based on age, gender, practice, and health care use. Within different chronic health conditions, we will determine inequalities in these health profiles by levels of health literacy, individual and neighbourhood measures of deprivation and occupational class, adjusting for age, gender, and recorded health care use and management (time since last consultation,

time since first recorded diagnosis, frequency of consultation and recorded pharmacological and non-pharmacological management in the last 12 months), again using appropriate regression models.

3) *Estimating healthy work life expectancy and the number of years with disability*. We will use EQ-5D data to classify health states and generate disability weights. Existing approaches (e.g. life tables and Interpolated Markov Chain (ImaCH) modelling[51]) will then be used to calculate the number of disability life years and healthy work life. The impact of long term health conditions on these estimates will be examined in stratified analysis. Regression analysis will be used to determine the impact of occupation, and other psychosocial determinants on the link between health conditions and estimates.

As with the primary research questions, the Spotlight Studies will have fully detailed pre-specified analyses defined and agreed within the research teams and involving the medical student.

3. ETHICAL CONSIDERATIONS

The survey questions do not cover sensitive topics and we do not anticipate any distress arising from completion of the survey.

Participants' personal data will only be accessible by authorised members of the research team during data collection phase of the trial. Personal data will only be received by the research team following consent by the study participant and will be held separately to research data. All trial databases and participant information are housed in the CTU Secure Network, which is a secure virtual network requiring Two Factor Authentication in order to access the data stored within there.

Roles and permissions are applied to users within the network as well as within an application to restrict what data a user can access and operations they can perform. The CTU Secure Network has been independently audited and achieved level one of the Government backed Cyber Essentials Scheme. Once data collection has been completed, all data will be maintained in such a form that they cannot be linked with identifiable participants and will be anonymised in the reports and for archival deposit.

There are secure physical storage arrangements for the hard copy at the Keele CTU within lockable filing cabinets. Completed consent forms will be securely stored separate to research data. In addition, any hard copy research data that has been printed for checking will be destroyed by shredding. Surveys will be stored without names and addresses for at least 5 years in accordance with Keele CTU standard operating procedures.

Before the start of the study, approval will be sought from a REC for the trial protocol, informed consent forms and other relevant documents. Substantial amendments that require review by REC and HRA will not be implemented until the REC and HRA grants a favourable opinion for the study (amendments may also need to be reviewed and accepted by the NHS R&D departments before they can be implemented in practice at sites). All correspondence with the REC and HRA will be retained in the Trial Master File.

An annual progress report (APR) will be submitted to the REC within 30 days of the anniversary date on which the favourable opinion was given, and annually until the trial is declared ended. It is the Chief Investigator's responsibility to produce the annual reports as required. The Chief Investigator will notify the REC of the end of the study. If the study is ended prematurely, the Chief Investigator will notify the REC, including the reasons for the premature termination. Within one year after the end of the study, the Chief Investigator will submit a final report with the results, including any publications/abstracts, to the REC.

4. DISSEMINATION AND IMPACT

Our success in disseminating research findings and achieving impact is underpinned by a systematic approach to developing research that can make a real difference to patients, healthcare providers and policy makers, coupled with a strategic approach to securing collaborations and partnerships which can support rapid roll-out and translation of the research findings. Dissemination is supported by the Primary Care Consortium Board where outputs of high quality research are disseminated to key stakeholders. The applicants, with PPIE involvement, will produce short reports on progress for Midlands Medicine. At a local level, we will produce regular updates via Clinical Commissioning Groups' (CCGs) newsletters, and through update meetings with R&D leads to influence local quality improvement and provide support for identifying outputs most relevant to the health needs of the local community. Educational slide sets will be prepared and be available for the Royal Colleges, professional bodies and medical charities. Additional knowledge mobilisation activities will be undertaken within the Research Institute's Impact Strategy in order to facilitate uptake by local services. We will seek advice from our PPIE groups to inform the dissemination plan to the public. In addition to posters reporting summary findings in participating practices we will host annual public dissemination events at Keele. Findings will be periodically posted on our study website and through social media using our established organisational Twitter account and blog.

5. MONITORING AND AUDIT

The study will follow the monitoring and audit procedures as set out in the Keele CTU Standard Operating Procedures and the Study Management Group will meet monthly to review study progress. A project steering committee will also be convened to provide project oversight.

6. REFERENCES

[1]GBD Study 2013 Collaborators. *Lancet.* 2015 Jun 7. [2]Vos et al. *Lancet.* 2012;380:2163-96. [3]Murray et al. *Lancet.* 2013;381:997-1020.[4]http://www.healthdata.org/. [5]van den Akker et al. *J Clin Epidemiol.* 1998;51:367-75. [6]Blyth et al. *Am J Prev Med.* 2015;49:98-101. [7]Naylor et al. The King's Fund, June 2015. [8]Brownson et al. *Ann Epidemiol.* 2015;25:458-65. [9]Khoury et al. *Cancer Epidemiol Biomarkers Prev.* 2013;22:508-16. [10]Violan et al. *PLoS One* 2014;9:e102149. [11]Porcheret et al. *J Am Med Inform Assoc.* 2004;11:78–86. [12]Jordan et al. *BJGP* 2007;57:7-14. [13]Jordan et al. *Ann Rheum Dis.* 2014;73:212-8. [14]Hughes et al. *Age Ageing* 2008;37:572-5. [15]Jordan et al. *BMC Musculoskel Dis.* 2010; 11. [16]Yu et al. *Rheumatology* 2015; Jul 9. [17]Strauss et al. *J Clin Epidemiol*. 2014;67:1163-71. [18]Roddy et al. *Rheumatology* 2010;49:105-111. [19]Bedson et al. *Eur J Pain.* 2013;17:434-443. [20]Helliwell et al. *BJGP*. 2013;63:e361-6. [21]Burton et al. *Fam Pract.* 2013;30:25-30. [22]Green et al. *Scand J Rheumatol.* 2014; 4:1-5. [23]Hayward et al. *BMJ Open.* 2015;5(6):e007355. [24]Institute of Medicine, 2014. [25]Jensen et al. *Med Care.* 2015;53:153-9. [26]Edwards et al. *Cochrane Database Syst Rev.* 2009 Jul 8;(3):MR000008. [27]McCluskey & Topping. *Perspect Public Health.* 2011;131:89-94. [28]Brooks R. *Health Policy.* 1996;37:53-72. [29]Von Korff et al. *Pain.* 1992;50:133-149. [30]Zigmond & Snaith. *Acta Psychiatr Scand.* 1983;67:361-370. [31]Yu et al. *Behav Sleep Med.* 2011;10:6-24. [32]PROMIS. hwww.nihpromis.org/ [33]McLennan et al. Dep. for Communities and Local Government, March 2011. [34]Smith et al. *Int J Behav Med.* 2008;15:194-200. [35]Wångdahl & Mårtensson. *Scand J Public Health.* 2014;42:25-31. [36]McGorrian et al. *Eur Heart J.* 2011;32:581-9. [37]www.jbs3risk.com/index.htm [38]Jordan et al. *Eur J Public Health,* 2014;24:396-8. [39]Prior et al. *BMC Health Serv Res* 2012;12:295. [40]Hayward et al. *BMJ Open.* 2015;5(6):e007355. [41]clinicalcodes.rss.mhs.man.ac.uk [42]Roberts et al. *BMJ Open.* 2014;4(7):e005429. [43]Mallen et al. *Prim Health Care Res Dev.* 2011;12:179-82. [44]www.aapor.org/AAPORKentico/Communications/ AAPOR-Journals/Standard-Definitions.aspx [45]Bennett et al. *PLoS Med.* 2010;8:e1001069. [46]Gorman et al. *AJE.* 2014;180:941-8. [47]Santin *et al. J Clin Epidemiol.* 2014;67:722-30. [48]Frankel et al. *BMJ Open.* 2012;2. pii: e000696. [49]Marshall et al. *OAC.* 2013;21:1674-84. [50]Islam et al. *PLoS One*. 2014;9:e83783. [51]Lievre et al. *J Nutr Health Aging.* 2007;11:508-14.

7. Appendix 1: *Study flowchart*