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| Host department: Nottingham |
| Project Title: |
| Exploring the care pathway to diagnosis for people with bullous pemphigoid |
| Proposed supervisory team: Primary supervisor:Dr Sonia Gran, Associate Professor of Medical Statistics, Centre of Evidence Based Dermatology, University of NottinghamExpertise: Medical statistics, routinely collected healthcare data and systematic reviewsCo-supervisors:Dr Laura Howells, Research Fellow and Health Psychologist, Centre of Evidence Based Dermatology, University of NottinghamExpertise: Health psychology and qualitative researchProfessor Matthew Ridd, GP and Professor of Primary Health Care, Centre of Academic Primary Care, University of Bristol,Expertise: Diagnosis and management of skin problems in primary careDr Karen Harman, Consultant Dermatologist, University Hospitals of Leicester NHS TrustExpertise: Autoimmune blistering diseases |
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| Potential for cross consortium networking and educational opportunities: |
| As one of the co-supervisors, Professor Ridd, is based at the University of Bristol, the PhD student will be able to spend some time and network with his research team. This will enable the student to gain experience and learn research skills from two different Schools of Primary Care. Professor Ridd also co-chairs the Society for Academic Primary Care Dermatology Research and NIHR SPCR Skin and Allergy working groups, providing opportunities to network and present/obtain feedback on proposed work and early findings. |
| Project description:Background Bullous pemphigoid (BP) is a serious autoimmune skin disease that results in large itchy blisters developing over the body and occurs most commonly in older people (over 70 years).1 Images of the disease can be found here: <https://dermnetnz.org/topics/bullous-pemphigoid-images.> Despite a threefold increase in mortality and poor quality of life, BP remains under-researched most probably as it is rare and there are few research champions.1,2 Dr Gran’s research group recently reported BP has an incidence of 7.63 per 100,000 person-years in England, is increasing worldwide, and is no longer rare in over 60 year olds.1,3  GPs are usually the first healthcare professionals patients with BP come into contact with but diagnosis is usually made by a dermatologist based on a combination of criteria, including typical clinical features and immunopathological findings. Bullous pemphigoid typically presents with intense itch and localised or generalised bullous lesions. Lesions predominately affect the inner parts of the limbs and the trunk. The period before typical bullae appearance usually lasts from a few months to years. For up to 20% of affected patients, bullae may be completely absent.4 What is the problem being addressed?  As BP is a rare condition (prevalence 48 per 100,000 people1) and may mimic other inflammatory dermatoses such as discoid eczema, contact dermatitis, senile pruritus, urticaria, nodular prurigo and scabies in the initial stages before blistering, there is potential for delayed referral by GPs to dermatologists (as these conditions are seen as less serious than BP) and consequently a delay in diagnosis (time between onset of symptoms and establishment of diagnosis). Diagnostic delay is multifactorial and can occur at patient, primary care and/or secondary care level. Therefore, it is important to explore the care pathway taking into account the experiences of patients, GPs and dermatologists.There is no cure for BP. The standard treatment for BP has traditionally been oral corticosteroids to control both the skin eruption and itch.5 Oral corticosteroids are known to have serious side-effects such as diabetes and osteoporpsis.6 We have recently reported, people with BP take oral steroids for long periods of time.7 Given BP is associated with treatment related co-morbidity and high mortality, diagnostic delay may impact prognosis and expose patients to unnecessary complications. Existing literature and rationale An international survey was conducted between 2017 and 2018 to explore and prioritise unmet needs in pemphigoid diseases from the perspective of patients, clinicians and researchers, in order to guide future research towards important research topics.10 A total of 135 participants were included (of which 71 were patients and 52 had bullous pemphigoid). Data on patient satisfaction showed that half of the patients were unsatisfied with patient care during the diagnostic process, mainly due to misdiagnosis and long diagnostic delay (mentioned by 88% of unsatisfied patients). Six patients visited more than 5 doctors before a correct diagnosis was made.8 In addition to the survey, there are several small retrospective hospital-based studies on delayed diagnosis in people with bullous pemphigoid (BP).4,9-12 The mean delay in diagnosis ranged between 6 and 29 months. However, to our knowledge, no study at population-level has been conducted and there are no reports in the literature which describe qualitative work with BP patients or healthcare professionals who look after them worldwide. A systematic review and case note review in this field are also lacking. This is unsurprising given that the condition is rare and primarily affects older people. This PhD project will therefore fill an important research gap and help optimise clinical practice. A recent multi-centre study has shown that patients with bullous pemphigoid respond better to treatment if diagnosed earlier.13 Finally, the government’s Rare Diseases Framework aims to “ensure that the lives of people living with rare disease continue to improve”. One of the top priorities of the framework include improving diagnosis.14Aim: To explore the care pathway to diagnosis for people with bullous pemphigoidObjectives1. To synthesise the current literature on what facilitates and delays diagnosis of BP
2. To determine the views of BP patients and healthcare professionals on the care pathway to diagnosis
3. To quantify conditions patients with BP may be misdiagnosed with and features that help distinguish BP at an early stage
4. To determine the average length of time for a diagnosis

MethodsStudy 1: Scoping review of the diagnostic pathway of BPA protocol will be written and registered with Prospero. Literature search: Ovid Medline and Ovid Embase.Inclusion criteria: Quantitative observational studies that have explored the diagnostic pathway in adults with bullous pemphigoid.Methods: Screening of titles/abstracts and full texts will be conducted by two people independently. The Joanna Briggs Institute risk of bias tool will be used for quality assessment.Analysis: Narrative and/or meta-analysis if data can be pooled (e.g. average time to diagnosis). MOOSE reporting guidelines will be used.15Study 2: Views and experiences of BP patients, GPs, and Dermatologists of the care pathway to diagnosis Study design: One-to-one interviews.  Study population: (i) A UK community-based sample of BP patients and (ii) GPs, and (iii) Dermatologists. Purposeful sampling will ensure a representation of gender, ethnicity, geographical location and length of diagnostic delay for (i), type, size and location of practice for (ii), and experience of BP for (iii).  Methods: Screening questionnaire to assess eligibility/record demographic factors of participants. One-hour one-to-one interviews (15 patients, 15 GPs and 15 Dermatologists) by telephone or Teams. Interviews will be semi-structured with open questions and the option to use patient vignettes and photos to prompt discussion. Patient vignettes and photos will be particularly useful for engaging GPs who have never seen a patient with bullous pemphigoid. One-to-one interviews facilitate in-depth exploration of personal experiencesand 15 interviews have been shown to be appropriate for the scope and design of this study.16,17 Data will be audio-recorded and transcribed using NVivo12. Patient partners will support interview topic guides and interpretation of the data.  Topics will be:   1. Experience of care pathway to diagnosis
2. Barriers and facilitators to diagnosis
3. Impact of their experiences and/or tools to help the pathway

 Analysis:  Framework analysis with a pre-defined theoretical framework. Participants may introduce new topics and areas of interest, and the framework will be adapted to include inductive coding as required. Standards for reporting qualitative research will be used.18 Please note that funding has been requested from the SPCR F6 round to conduct interviews with GPs as a standalone project (outcome in December 2022). If the latter is successful, this PhD project with conduct interviews with advanced nurse practitioners and community nurses instead of GPs.Study 3: Review of GP notes  Study design: Retrospective case note review   Sampling source: A purposeful sample of GP Practices who have patients with BP from three different areas in England (Nottingham, Coventry and Manchester) using the NIHR’s Clinical Research Network. The broadness of this group and the diversity of the geographical areas will ensure good external validity. If necessary, we will also ask the Skin Research in Primary Care Group and the Primary Care Dermatology Society to help recruit GPs. Purposeful sampling will ensure a representation of urban/rural location, practice size (according to patient list) and type (research/teaching/other), and subsequently ‘information-rich’ practices.19At least 25 practices will be recruited. It is estimated that 4 BP patients per GP practice are diagnosed per year.7Study population: 100 adults diagnosed with BP. Methods: The PhD student will review the notes using a tested and anonymised case report form (CRF) to obtain information on clinical diagnoses and symptoms identified prior to BP and their dates. For validation purposes, a GP from the patient’s practice and direct team will review the first 10% of the case notes independently and differences will be discussed. The GPs will be paid for their time.   Analysis: Description of symptoms/conditions in BP patients that could lead to misdiagnosis or features that may help distinguish BP at an early stage (informed by studies 1 and 2); average delay in diagnosis (time between onset of symptoms and establishment of diagnosis); reason for delay.   Study 4: Exploration of conditions/symptoms BP patients could be misdiagnosed with, and length of diagnostic delay  Data source: The Clinical Practice Research Datalink (CPRD) contains the prospective medical records of over 24 million UK patients. Data are broadly representative of the demographics including ethnicity of the UK population and have a high validity of recorded diagnoses using Read codes.20 GOLD and AURUM versions will be used.21 Study design: Case-control  Study population: Incident adult BP cases identified using a validated algorithm between 1998 and 2022.22Controls: Age, sex and practice individually matched patients who do not have a record of BP anywhere in their records. A pseudo-diagnosis date will be the diagnostic date of their matched case.   Outcome: Incident consultations for discoid eczema, contact dermatitis, senile pruritus, urticaria, nodular prurigo and scabies (plus any additional diagnoses/symptoms identified in studies 1 and 2) in the first 3 years prior to the first BP/pseudo-diagnosis date. The cut-off of 3 years may change depending on the results from studies 1 to 3.Analysis: Descriptive statistics. Conditional logistic regression to determine odds of events associated with BP misdiagnosis prior to diagnosis in cases compared to controls (unadjusted and adjusted). Diagnostic delay in cases will be calculated as the difference between first potential misclassification diagnosis (based on exposures listed above) and first BP diagnosis date. The median (IQR) delay will be calculated.   Confounders: Charlson comorbidity index, deprivation and ethnicity. Sample size: Approximately 10000 incident patients with BP exist in the CPRD with >3 years’ data prior to diagnosis. A ratio of 1:5 controls (with >3 years’ data) will be used. There will be >90% power to detect a difference in odds of events between cases and controls of at least 5%, at the 5% level of significance.  RECORD reporting guidelines will be used.23ImpactUsing the NIHR's impact plan the project will achieve the following impact24:In the short-term, (i.e., within 1 year of study completion), through dissemination routes mentioned below: 1. a greater awareness of the care pathway to diagnosis for bullous pemphigoid
2. updated national guidelines to improve the care pathway to diagnosis for bullous pemphigoid

In the long-term, (i.e., within 5 years of study completion), after further funding:1. The development of a diagnostic tool for rare autoimmune blistering skin diseases for GPs
2. The implementation of an educational program for GPs on rare autoimmune blistering skin diseases

By improving knowledge on the clinical pathway to diagnosis, this proposed study will have the following key benefits for patients with bullous pemphigoid:* Patients may respond to milder treatment if diagnosed earlier
* Earlier diagnosis and response to milder treatment may reduce side-effects
* Patients will not receive unnecessary treatment for misdiagnosed conditions
* Patients may not require hospitalisation.

All of the above will improve efficiency and reduce costs for the NHS.Dissemination routes that will be used:Key findings will be disseminated widely to members of the scientific community, clinicians, professional bodies, community groups and patients and the public using the following established dissemination routes. The PhD student will work in collaboration with the patient partners to disseminate key findings via PEM Friends.* Scientific presentation at one of the leading UK general practice conferences (e.g., Royal College of General Practitioners’ annual conference).
* Key findings will be sent to the Royal College of General Practitioners, British Association of Dermatologists, the Society for Academic Primary Care Dermatology Research Group, Primary Care Dermatology Society, PEM Friends and International Pemphigus & Pemphigoid Foundation (IPPF) support groups
* Lay summary for the following websites: NIHR School of Primary Care, PEM Friends and International Pemphigus and Pemphigoid Foundation, PEM Friends’ Facebook (>150 followers)
* Key findings will be sent to the Centre of Evidence Based Dermatology’s (CEBD) mailing list (>1000 members)
* Key findings will be sent to the CEBD, IPPF and PEM Friends’ Twitter accounts
* University of Nottingham’s press office will arrange an interview with BBC Nottingham.

The results will also be published (Open Access) in leading peer reviewed journals in general practice (e.g. British Journal of General Practice) or dermatology (e.g. British Journal of Dermatology).References1.Persson M, Harman K, Vinogradova Y et al. Prevalence and mortality of bullous pemphigoid in England 1998–2017: a population-based cohort study. Br J Dermatol. 2021; 184: 68-77.  2. Kouris A, Platsidaki A, Christodoulou C et al. Quality of life, depression, anxiety and loneliness in patients with bullous pemphigoid. A case control study. An Bras Dermatol. 2016; 91(5):601-603. 3.Persson M, Begum N, Grainge M et al. The global incidence of bullous  pemphigoid: a systematic review and meta-analysis. Br J Dermatol. 2022; 186:  414-425. 4. della Torre R, Comberscure C, Cortes B et al. Clinical presentation and diagnostic delay in bullous pemphigoid: a prospective nationwide cohort. Epid & Health. Serv Res. 2012; 167:1111-1117. 5. Whittaker S, Marsden J, Spittle M et al. Joint British Association of Dermatologists and U.K. Cutaneous Lymphoma Group guidelines for the management of primary cutaneous T-cell lymphomas. British Journal of Dermatology. 2003;149: 1095-1107. 6. Van Staa TP, Leufkens HGM, Abenhaim L et al. Use of Oral Corticosteroids and Risk of Fractures. J Bone Miner Res. 2000; 15: 993-1000. 7. Persson M, Harman H, Thomas K, Chalmers J, Vinogradoca Y, Langan SM, Hippisley-Cox, Gran S. Long-term oral prednisolone exposure for bullous pemphigoid in primary care: a population-based study. Br J of Gen Practice. 2021; 71 (713);e904-e911. 8. Lamberts A, Yale M, Grando SA et al. Unmet needs in pemhigoid diseases: an international sruvey amongst patients, clinicians and researchers. Acta Derm Venereol. 2019; 99:224-225. 9. Zhang Y, Luo Y, Han Y et al. Non-bullous lesions as the first manifestation of bullous pemphigoid: A retrospective analysis of 181 cases. J Dermatol. 2017; 44(7):742-746. 10. Lamberts A, Meijer JM, Pas HH et al. Nonbullous pemphigoid: Insights in clinical and diagnostic findings, treatment responses and prognosis. J Am Acad Dermatol. 2019; 81: 355-363. 11. Sun C, Chang B, Gu H. Non-bullous lesions as the first manifestation of bullous pemphigoid: a retrospective analysis of 24 cases. J Dermatology Treat. 2009; 20:233-237. 12. Zhou X & Li H. Clinical Analysis of 89 Cases of Bullous Pemphigoid. Chinese Journal of Dermatology. 1994; 6. 13. Williams HC, Wojnarowska F, Kirtschig G et al. Doxycycline versus prednisolone as an initial treatment strategy for bullous pemphigoid: a pragmatic, non-inferiority, randomised controlled trial. The Lancet. 2017; 389:1630-38.14. Internet: UK Rare Diseases Framework - GOV.UK (www.gov.uk) (https://www.gov.uk/government/publications/uk-rare-diseases-framework) [Last accessed 2nd September 2022] 15. Brooke BS, Schwartz TA, Pawlik TM. MOOSE Reporting Guidelines for Meta-analyses of Observational Studies. JAMA Surg. 2021 Aug 1;156(8):787-788. doi: 10.1001/jamasurg.2021.0522. PMID: 33825847.16. Ryan F, Coughlan M, Cronin P. Interviewing in qualitative research: The one-to-one interview. Int J Therapy and Rehab. 2009 16:6, 309-314.17. Sandelowski M. Sample size in qualitative research. Res Nurs Health. 1995;18. Tong A, Sainsbury P, Craig J. Consolidated criteria for reporting qualitative research (COREQ): a 32-item checklist for interviews and focus groups. International Journal for Quality in Health Care. 2007; 19(6); 349–35719. Luborsky MR, Rubinstein RL. Sampling in qualitative research: rationale, issues. and methods Res Aging. 1995;17(1):89–113.20. Herrett E, Thomas SL, Schoonen WM, Smeeth L, Hall AJ. Validation and validity of diagnoses in the General Practice Research Database: a systematic review. Br J Clin Pharmacol. 2010;69(1):4-14.21. Internet: https://www.cprd.com [Last accessed 2nd September 2022] 22. Persson MSM, Harman KE, Vinogradova Y, Langan SM, Hippisley-Cox J, Thomas KS, Gran S.  Validation of bullous pemphigoid and pemphigus vulgaris recording in routinely collected electronic primary healthcare records in England. BMJ Open. 2020; doi: 10.1136/bmjopen-2019-035934  23. Internet: [RECORD Reporting Guidelines (record-statement.org)](http://www.record-statement.org/) (<https://www.record-statement.org>) [Last accessed 2nd September 2022]   |

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| Training and development provision by host: |
| **Formal training:**This PhD project will use a mixed methods approach and provide the PhD student with opportunities to gain important research skills in qualitative research, the use of routinely collected healthcare records, medical statistics and systematic reviews. The student will also obtain a good foundation in evidence-based medicine which will help their future career.The following modules which are part of the University of Nottingham’s Master’s of Public Health programme will be undertaken by the PhD Student at the appropriate time over the 3 years:Qualitative Research (10 credits)Systematic Reviews (10 credits)Data Organisation and Management in Epidemiology in R (10 credits) |
| **Informal training:** The PhD student will be hosted at the Centre of Evidence Based Dermatology (CEBD) within the School of Medicine (SoM) at the University of Nottingham. The CEBD has successfully supported over 15 PhD students to date who have all subsequently obtained professional careers. The CEBD hosts the editorial base for the Cochrane Skin Group and is co-directed by Professor Hywel Williams (former Director of the NIHR HTA programme and NIHR Senior Investigator) and Professor Kim Thomas, and generates 40-50 peer-reviewed publications per year, with over £6 million in grant income in the last 5 years.The experienced supervisory team will provide expertise in primary care, database epidemiology, blistering diseases, systematic reviews, and qualitative work. The supervisory team will support the student with monthly meetings throughout the project (additional meetings will also be provided, as and when needed).The student will be joining a vibrant community of PhD students with many opportunities for learning/support and career progression within the SoM. The SoM operates a mentorship programme, peer support and grant writing training for PhD students, and provides methodological training through its N-trans programme and a regular programme of workshops and seminars. PhD students are provided opportunities to assist with teaching activities and are encouraged to network across the SoM. There is a requirement to present their work in the final year of their studies to members of the Doctoral Training Programme. They are also encouraged to attend workshops on career development.The University of Nottingham provides several short courses for PhD students including critical appraisal, writing up a thesis, preparing for a viva voce, presentation skills, qualitative and statistical packages, leadership skills and research integrity.The CEBD will provide the PhD student training skills to run patient and public involvement and engagement workshops (see below for further details).The student will be provided with a high-tech PC and have access to Stata, R and NVivo. They will also be encouraged to attend external training courses (according to their needs) and present at national and international scientific conferences. |
| **PPIE:** We have convened the following (patient and public involvement and engagement) PPIE steering group for the PhD student to lead:Ingrid Thompson who has had bullous pemphigoid for over 7 years and experienced a long delay before diagnosisIsobel Davies who has had mucous membrane pemphigoid for over 20 years and is the spokesperson for the support group PEM Friends (http://pemfriendsuk.co.uk/)Sue Norris who was diagnosed with bullous pemphigoid in 2021 following her Covid-19 vaccination.This group is appropriate as it covers patient perspectives and representation of the main UK patient support group in this area. Two of the patients have different experiences of diagnosis of BP. The group will be involved throughout the project and will help by (i) reviewing and commenting on the protocols, interview topic guides, and the results; and (ii) by disseminating the results to the patient community with a lay summary of the results and short video clips; and (iii) planning future research proposals. Patient partner time will be paid according to NIHR guidelines. There will be five PPI workshops throughout this project.  The Centre of Evidence Based Dermatology (CEBD) holds an annual patient panel training workshop to provide networking opportunities, and shared learning for patients involved in dermatological research. The CEBD strives to meet the National Standards for Public Involvement developed by the NIHR and have recently reviewed procedures in the light of updated guidance. The PPIE steering group for this PhD project will be invited to this annual event for training purposes. |