Using electronic health records to inform trial feasibility in a rare autoimmune blistering skin disease in England

M. S. M. Persson¹, K. E. Harman¹, K. S. Thomas¹, J. R. Chalmers¹, Y. Vinogradova², S. M. Langan³, J. Hippsley-Cox⁴ and S. Gran¹*

Abstract

Background: Trials of novel agents are required to improve the care of patients with rare diseases, but trial feasibility may be uncertain due to concerns over insufficient patient numbers. We aimed to determine the size of the pool of potential participants in England 2015–2017 for trials in the autoimmune blistering skin disease bullous pemphigoid.

Methods: The size of the pool of potential participants was estimated using routinely collected healthcare data from linked primary care (Clinical Practice Research Datalink; CPRD) and secondary care (Hospital Episode Statistics; HES) databases. Thirteen consultant dermatologists were surveyed to determine the likelihood that a patient would be eligible for a trial based on the presence of cautions or contra-indications to prednisolone use. These criteria were applied to determine how they influenced the potential pool of participants.

Results: Extrapolated to the population of England, we would expect approximately 10,800 (point estimate 10,747; 95% CI 7191 to 17,239) new cases of bullous pemphigoid to be identified in a three-year period. For a future trial involving oral prednisolone (standard care), the application of cautions to its use as exclusion criteria would result in approximately 365 potential participants unlikely to be recruited, a further 5332 could be recruited with caution, and 5104 in whom recruitment is still possible. 11–17% of potential participants may have pre-existing dementia and require an alternative consent process.

Conclusions: Routinely collected electronic health records can be used to inform the feasibility of clinical trials in rare diseases, such as whether recruitment is feasible nationally and how long recruitment might take to meet recruitment targets. Future trials of bullous pemphigoid in England may use the data presented to inform trial design, including eligibility criteria and consent processes for enrolling people with dementia.

Keywords: Bullous pemphigoid, Electronic health records, Clinical practice research Datalink, Oral prednisolone, Hospital episode Statistics, Trial design, Rare disease

* Correspondence: sonia.gran@nottingham.ac.uk

¹Centre of Evidence Based Dermatology, School of Medicine, University of Nottingham, Nottingham, UK

© The Author(s). 2021 Open Access This article is licensed under a Creative Commons Attribution 4.0 International License, which permits use, sharing, adaptation, distribution and reproduction in any medium or format, as long as you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons licence, and indicate if changes were made. The images or other third party material in this article are included in the article’s Creative Commons licence, unless indicated otherwise in a credit line to the material. If material is not included in the article’s Creative Commons licence and your intended use is not permitted by statutory regulation or exceeds the permitted use, you will need to obtain permission directly from the copyright holder. To view a copy of this licence, visit http://creativecommons.org/licenses/by/4.0/. The Creative Commons Public Domain Dedication waiver (http://creativecommons.org/publicdomain/zero/1.0/) applies to the data made available in this article, unless otherwise stated in a credit line to the data.
Background
Bullous pemphigoid is a rare blistering skin disease that predominantly affects older people [1]. Following a diagnosis of bullous pemphigoid, individuals affected are almost three times more likely to die than their peers [1]. Current treatment regimens are often based on oral prednisolone, which has been the mainstay of treatment for decades. Oral prednisolone is effective in treating blisters, but may lead to the development or exacerbation of potentially life-limiting diseases such as diabetes mellitus and infections [2, 3]. Trials of novel agents are required in order to improve patient management, [4] however, the pool of potentially eligible patients in the UK is currently unknown.

Routinely collected electronic health records (EHR) can be used to inform trial feasibility and guide trial development. Many rare diseases are in need of clinical trials of new treatments, however, it is difficult to proceed with trial planning and design without first knowing if there are enough people to make such a trial feasible. The present work focuses on bullous pemphigoid, but the methodology used may be relevant to a multitude of rare diseases.

Using EHR, we aimed to estimate the number of new cases of bullous pemphigoid over a three-year period in England and to determine how many of these patients were affected by conditions that may exclude them from participating in a trial assuming a control arm treated with 0.5 mg/kg oral prednisolone (considered standard care).

Methods
Study design
This was a descriptive study, reported using RECORD guidelines for the reporting of studies conducted using observational routinely collected health data [5].

Data sources
Two linked data sources were utilised: primary care data from the Clinical Practice Research Datalink (CPRD) GOLD and secondary care data from the Hospital Episode Statistics (HES).

The CPRD GOLD is a longitudinal database that contains the anonymised healthcare records for UK general practices using the Vision software system. Within the CPRD, clinical data from consultations, hospital discharge letters, and specialist clinic letters are recorded using Read codes [6, 7].

Linked data are available from HES admitted patient care for approximately 75% of the English practices within the CPRD, covering approximately 10 million people. Within the HES admitted patient care, diagnoses from each hospitalisation episode are recorded using the International Classification of Diseases version 10 (ICD-10) and procedures are recorded using the Office of Population Censuses and Surveys Classification of Interventions and Procedures (OPCS version 4.6).

Observation period
The three-year study included two observation periods: one observation period for the calculation of the incidence rate and one for the application of trial exclusion criteria to the population of incident cases, described below.

For the incidence calculation, the observation period commenced on the latest of (i) 1 January 2015, (ii) 12 months after the date the patient registered with their current practice, (iii) the date the patient’s practice was declared up-to-standard (i.e., date assigned on completion of regular audits confirming data quality), or (iv) the patient’s 18th birthday. The observation period terminated on the earliest of (i) 31 December 2017, (ii) the
date of death, (iii) the date the patient left the practice, (iv) the practice’s last data collection date, or (v) the most recent linkage date between the CPRD and HES.

When applying the trial exclusion criteria to incident cases, only data prior to the bullous pemphigoid index date were examined. Therefore the observation period commenced on the practice’s up-to-standard date and terminated on the index date for bullous pemphigoid.

Definitions of exclusion criteria
Contra-indications or cautions to oral prednisolone use were identified from those listed in the British National Formulary (BNF, 2020) [3]. A total of 2 contra-indications and 19 cautions were identified. An additional caution, malignancy (excluding basal cell carcinoma, BCC), was added to the list as it is an exclusion criteria that has previously been implemented in clinical trials of oral corticosteroid in bullous pemphigoid [10, 11]. Based on the guidance in the BNF and clinical expertise, each contraindication was coupled to a specified timeframe of relevance, relative to the bullous pemphigoid index date (Table 1). For example, receiving a varicella zoster vaccine was only a contra-indication to oral prednisolone use if it occurred in the three months preceding the bullous pemphigoid index date. Conversely, osteoporosis was considered a caution if it occurred any time before the bullous pemphigoid date.

Using an online survey (Microsoft Office Forms), 13 consultant dermatologists experienced in managing bullous pemphigoid graded whether they were “very likely”, “somewhat likely”, or “unlikely” to exclude a person from a trial involving oral prednisolone if they had a history of any of the 22 conditions within the specified time frames. The dermatologists were all UK-based and identified based on their involvement with the British Association of Dermatologists guidelines for the management of pemphigus vulgaris and bullous pemphigoid or the Pemphigoid and Pemphigus Priority Setting Partnership.

Table 1 Conditions listed as cautions to the use of oral corticosteroids in the British National Formulary and the number (proportion) of incident cases of bullous pemphigoid with a record for each caution within specified timelines. Presented alongside the recruitment status associated with having that condition when considering a clinical trial involving 0.5 mg/kg oral prednisolone

| Caution                     | Timeline*                        | N (%) of cases | Recruitment status** |
|-----------------------------|----------------------------------|----------------|----------------------|
| Total incident cases        | 237                              |                |                      |
| Diabetes mellitus           | Any time before                  | 55 (23.2%)     | Recruit with caution |
| Diverticulitis              | In 1 year before                 | 0              | Possible             |
| Epilepsy                    | Any time before                  | 12 (5.1%)      | Possible             |
| Glaucoma                    | Any time before                  | 16 (6.8%)      | Recruit with caution |
| Heart failure               | Any time before                  | 43 (18.1%)     | Recruit with caution |
| Hypertension                | Any time before                  | 159 (67.1%)    | Possible             |
| Hypothyroidism              | Any time before                  | 30 (12.7%)     | Possible             |
| Intestinal anastomosis      | In 6 months before               | 1 (0.4%)       | Unlikely             |
| Malignancy (excluding BCC)  | In 5 years before                | 23 (9.7%)      | Possible             |
| Myasthenia gravis           | Any time before                  | 1 (0.4%)       | Possible             |
| Myocardial infarction       | In 6 months before               | 3 (1.3%)       | Recruit with caution |
| Myopathy                    | Any time before                  | 1 (0.4%)       | Recruit with caution |
| Ocular herpes simplex       | Any time before                  | 1 (0.4%)       | Unlikely             |
| Osteoporosis                | Any time before                  | 38 (16.0%)     | Recruit with caution |
| Peptic ulcer                | In 1 year before                 | 2 (0.8%)       | Recruit with caution |
| Septicaemia/sepsis          | In 3 months before               | 3 (1.3%)       | Unlikely             |
| Severe mental illness       | In 10 years before               | 1 (0.4%)       | Recruit with caution |
| Systemic sclerosis          | Any time before                  | 0              | Possible             |
| Venous thromboembolic disorders | Any time before               | 19 (8.0%)      | Possible             |
| Tuberculosis                | Any time before                  | 3 (1.3%)       | Unlikely             |
| Ulcerative colitis          | In 5 years before                | 2 (0.8%)       | Possible             |
| Varicella zoster vaccine    | In 3 months before               | 4 (1.7%)       | Recruit with caution |

* Timeline relative to bullous pemphigoid index date
** Recruitment status was determined by the category chosen by > 50% of the consultant dermatologists in the online survey: Possible (> 50% classed the caution unlikely to lead to exclusion), recruit with caution (> 50% classed the caution very or somewhat likely to lead to exclusion, note that < 50% considered it very likely), or unlikely (> 50% classed the caution as very likely to lead to exclusion)
Responses were pooled and where there were discrepancies, the caution was classified in accordance with the category chosen by >50% of dermatologists. This was felt to be a reasonable cut-off for determining consensus.

**Code lists for exclusion criteria and dementia**

Code lists were developed for the 22 cautions/contraindications considered potential exclusion criteria for a trial involving oral prednisolone and for dementia. Since bullous pemphigoid generally affects older people, where the prevalence of dementia is increased, [12] it was felt important to identify pre-existing dementia, as well as prednisolone cautions, to provide an indication of the proportion of patients with capacity to consent.

Primary care and secondary care code lists were developed for each caution based on published Read and ICD-10 lists, respectively. The code lists were primarily drawn from the work of Kuan et al., [12] a study of 308 physical and mental health conditions, as this allowed a consistent approach to be applied across all conditions, and were modified and supplemented as required. For example, only codes from the CALIBER “Thyroid disease” category that indicated decreased thyroid function were used for hypothyroidism in the current work. Additionally, the code lists for cautions coupled with a limited time frame (e.g., six months before bullous pemphigoid) were manually reviewed and codes stating “history of” or similar were excluded.

The code lists were supplemented with Read, ICD-10, and OPCS codes generated through manual searching of the data dictionaries. Finally, varicella zoster code lists involving product and vaccination codes were drawn from the work of Jain et al., [13]. Code lists were reviewed in conjunction with a consultant dermatologist (KEH) to ensure suitability and clinical relevance. Full code lists are available in the Additional File 1.

**Identification of exclusion criteria and dementia**

The code lists were applied to the CPRD clinical, referral, test, therapy, and immunisation data and HES admitted patient care and OPCS data. For cautions with a time frame of “any time before bullous pemphigoid”, all codes prior to the bullous pemphigoid index date were identified. For conditions with a limited time frame (e.g., in the “x months” before bullous pemphigoid) only codes that occurred in the “x months” before bullous pemphigoid, but at least 12 months after the patient’s current registration date were examined. The time limit of 12 months after the patient’s current registration date was used to exclude potential historic events entered on transfer to a new general practice.

**Statistical analysis**

The incidence rate of bullous pemphigoid was determined per 100,000 person-years using previously published methods [1]. Age-specific incidence rates were calculated for five-year age bands. These were applied to the Office for National Statistics population estimate for England [14] over the same time period to estimate the total number of new cases that might be expected in England.

Of the incident cases, the number and proportion with a record for each of the cautions within the specified time frame was determined. The proportion of patients with conditions that were unlikely to allow recruitment (recruitment unlikely group), that would be possible to recruit with caution (recruit with caution group), and that would be possible to recruit (recruitment possible group) were determined. For each category, the proportion with pre-existing dementia were determined. The proportions were applied to the estimated number of new cases in England 2015–2017. Analyses were conducted with Stata 16 (2019; StataCorp LLC, College Station, TX, USA).

**Ethical approval**

The present study was approved by the Independent Scientific Advisory Committee for the CPRD (ISAC protocol no 18_224).

**Results**

**Classification of recruitment status from survey**

Of the 22 conditions considered to be contraindications or cautions, four were categorised as recruitment unlikely (>50% of dermatologists considered the disease “very likely” to lead to exclusion), nine were recruit with caution (>50% of dermatologists considered the condition “very likely” or “somewhat likely” to lead to exclusion; but <50% of dermatologists considered the disease “very likely”), and nine were recruitment possible (>50% of dermatologists considered the condition “unlikely” to lead to exclusion).

**Study population**

Between 2015 and 2017, 237 incident cases of bullous pemphigoid were identified in the CPRD and HES (Additional File 2). The median age when the diagnosis of bullous pemphigoid was first recorded was 78.7 years (IQR 70.9 to 87.2). 134 (56.5%) of those affected were women.

**Incidence of bullous pemphigoid 2015–2017**

The incidence of bullous pemphigoid was 8.4 (95%CI 7.4 to 9.5) per 100,000 person-years. The age-specific incidence rates of bullous pemphigoid per age category are available in the Additional File 3. Extrapolated to the
population of England there would be an estimated 10,800 (point estimate 10,747; 95% CI 7191 to 17,239) new cases in England in a three-year period.

Cautions to oral prednisolone use
Of the incident cases, 44 (18.6%) had no recorded cautions to the use of oral prednisolone. Conversely, 193 (81.4%) had a record for at least one caution to oral prednisolone use. The commonest comorbidities considered cautions to the use of prednisolone and present at the time the diagnosis of bullous pemphigoid was first recorded were hypertension (67.1%), diabetes mellitus (23.2%), heart failure (18.1%), and osteoporosis (16.0%) (Table 1).

Classification of population by recruitment status
Across the incident cases, 112 (47.3%) patients were considered possible to recruit (no caution or only cautions unlikely to lead to exclusion), 117 (49.4%) could be recruited with caution, and 8 (3.4%) would be unlikely to be recruited to a trial of oral prednisolone. Extrapolated to the population of England in 2015 to 2017, approximately 5104 would be possible to recruit and an additional 5332 could be recruited with caution. However, 365 of incident cases would be unlikely to be recruited due to cautions to the use of oral prednisolone. Of these, 911 (17.9%), 592 (11.1%), and 46 (12.5%), respectively, may have pre-existing dementia (Table 2).

Discussion
We have described a novel use of EHRs, such as the CPRD and HES, for the planning of clinical trials in rare diseases. Although this approach has been on the agenda for years, few publications incorporate this process in trial planning. We have shown that data from EHRs may be useful for determining whether conducting a trial for a rare disease is feasible nationally, how many practices might need to be approached, and how long recruitment might take to meet recruitment targets. In addition, linked EHR data can be used to determine how the pool of eligible participants changes according to how trial eligibility criteria are implemented.

We suggest the following considerations when using EHR to plan the design and conduct of a trial. Firstly, it should be possible to reliably identify the disease of interest from the EHR available. Such validation work is essential to ensure that the work captures patients with the disease of interest. Secondly, consideration needs to be paid to the comorbidities examined. We chose a broad approach that might be useful for a variety of new treatments, assuming the trials use oral prednisolone as the comparator. In the future, researchers may choose to use criteria that relate specifically to their research question, treatments of interest, and sample size requirements. Finally, the benefits of conducting such a study may be beneficial also during the conduct of a trial. The characteristics of the population of potentially eligible participants identified via EHR can be compared with current recruitment patterns to determine the generalisability of the study population and identify areas for improvement in the recruitment strategy.

For bullous pemphigoid, we have shown that pre-existing comorbidities that are considered cautions to oral prednisolone use are common at the time of diagnosis of bullous pemphigoid. As many as 81.4% of patients have at least one caution that may make them ineligible for a clinical trial if all cautions were considered as exclusion criteria. This highlights that the balance between the safety of included patients and the impact on the generalisability of trial results needs to be considered. Finally, we have shown that trial planning should consider patients with dementia, as about one in six patients may have pre-existing dementia.

In keeping with the literature, cardiovascular comorbidities, and hypertension in particular, are common amongst people with bullous pemphigoid. Indeed, comorbidities in general were common amongst the population, which is reflective of the fact that bullous pemphigoid most often affects older people [1]. Previous work has shown that conditions such as hypertension, malignancies, diverticular disease, heart failure, and mental illnesses are common amongst the older population that is also most susceptible to bullous pemphigoid. However, not all comorbidities make a patient ineligible. In a recent clinical trial involving oral prednisolone in patients with bullous pemphigoid, approximately 9% of individuals assessed for eligibility were excluded on the grounds of “substantial comorbidities”. This significant proportion suggests that in practice, clinicians assessing patients for eligibility to a clinical trial may choose to exclude not only the 3.4% we deemed ineligible, but also a proportion of those we considered could be recruited with caution.

A limitation of our work is the inability to determine the severity of either the bullous pemphigoid or the caution, which are vital for clinical decision-making regarding trial eligibility. Furthermore, we have not been able to ascertain whether or not the cautions identified from

### Table 2 Number (proportion) of the incident cases of bullous pemphigoid with and without pre-existing dementia according to their recruitment status

| Recruitment status       | N   | With dementia | Without dementia |
|--------------------------|-----|---------------|------------------|
| All patients             | 237 | 34 (14.4%)    | 203 (85.7%)      |
| Recruitment possible     | 112 | 20 (17.9%)    | 92 (82.1%)       |
| Recruit with caution     | 117 | 13 (11.1%)    | 104 (88.9%)      |
| Recruitment unlikely     | 8   | 1 (12.5%)     | 7 (87.5%)        |
the CPRD and HES relate to therapy. It is possible that oral prednisolone therapy was commenced in specialist dermatology clinics prior to the recording of bullous pemphigoid in the CPRD or HES and a small proportion of the cautions observed, such as diabetes and osteoporosis, may be a consequence of the initial therapy. Additionally, although we used both primary (CPRD) and secondary care (HES) records to identify comorbidities, the true number may be underestimated (resulting in a misclassification bias) if patients have not sought medical treatment for their condition or if the information has not been recorded. However, we believe this number is likely to be small and largely limited to conditions with minor symptoms. The 13 consultant dermatologists whose views shaped the classification of cautions were chosen based on their experience in the area, but may not be representative of all dermatologists that may be involved in trial recruitment in the UK. Also, the data drawn were from England and may not be representative of other populations. Finally, our findings are based on a relatively small number of patients identified in the CPRD and HES over the most recent three-year period for which the data were available. Expanding the observation period would have increased the numbers, but was felt to reduce the applicability of findings to future trials as disease recording and patient characteristics may have changed over time.

Conclusions
In conclusion, we have used EHR to guide the design and implementation of a clinical trial in bullous pemphigoid. We have provided an estimation of the number of people that may be available to recruit to a trial involving oral prednisolone. Researchers may use our findings to determine the feasibility of conducting a clinical trial of bullous pemphigoid in England based on their specific sample size parameters. We suggest, however, that recruitment is likely to be challenging and eligibility criteria should be broad to ensure generalisable results.

Acknowledgments
We acknowledge the following consultant dermatologists for their contribution to the online survey: Doctors Krishna S Mukkanna, Karen E Harman, Richard Groves, Jane Setterfield, Susannah Fraser, Kara Heelan, Ruth Murphy, Philip Hampton, P D Yesudian, Sneath M Langan, Mahbub M U Chowdhury, Gudula Kirtschig, and Antonia Lloyd-Lavery. This study is based in part on data from the Clinical Practice Research Datalink obtained under licence from the UK Medicines and Healthcare Products Regulatory Agency. The data is provided by patients and collected by the National Health Service as part of their care and support. Hospital Episode Statistics and Office of National Statistics data, 2019©, is re-used with the permission of The Health & Social Care Information Centre. All rights reserved. The interpretation and conclusions contained in this study are those of the authors alone.

Authors’ contributions
MSMP conceived and planned the design of the work, developed the code lists, analysed the data, interpreted the findings, and drafted and revised the paper. KEH was involved in the conception and design of the work, revision of the code lists, interpretation of the findings, and revision of the paper. KST was involved in the conception of the work, interpretation of the findings, and revision of the paper. JRC was involved in the conception of the work, interpretation of the findings, and revision of the paper. YY was involved in the design of the work, data extraction, interpretation of the findings, and revision of the paper. JH-C was involved in the design of the work, interpretation of the findings, and revision of the paper. SG conceived and planned the design of the work, assisted in the analysis of the data, interpreted the findings, and revised the paper. All authors have read and approved the manuscript.

Funding
This paper presents independent research funded by the National Institute for Health Research (NIHR) under its Research for Patient Benefit Programme (Grant Reference Number PB-PG-0817-20033). The views expressed are those of the author(s) and not necessarily those of the NIHR or the Department of Health and Social Care. SML reports grants from Wellcome Senior Clinical Fellowship in Science (205039/Z/16/Z) during the conduct of the study. The funding bodies had no role in the design of the study, collection, analysis, interpretation of data or in writing the manuscript.

Availability of data and materials
The data that support the findings of this study are available from the CPRD (www.cprd.com) but restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available. Data are however available from the authors upon reasonable request and with permission of the CPRD.

Ethics approval and consent to participate
The present study was approved by the Independent Scientific Advisory Committee for the CPRD (ISAC protocol no 18_224).

Consent for publication
Not applicable.

Competing interests
The authors declare no conflicts of interest.

Author details
1Centre of Evidence Based Dermatology, School of Medicine, University of Nottingham, Nottingham, UK. 2Division of Primary Care, University of Nottingham, Nottingham, UK. 3Department of Non-communicable Disease Epidemiology, London School of Hygiene and Tropical Medicine, London, UK. 4Nuffield Department of Primary Care Health Sciences, University of Oxford, Oxford, UK.

Supplementary Information
The online version contains supplementary material available at https://doi.org/10.1186/s12874-021-01212-1.

Additional file 1: Code lists used for the 22 cautions to oral prednisolone use
Additional file 2: Identification of incident cases of bullous pemphigoid in HES-linked CPRD practices and HES admitted patient care in England 2015–2017
Additional file 3: Incidence rate of bullous pemphigoid per 100,000 person-years in England 2015–2017 by age category

Abbreviations
CPRD: Clinical Practice Research Datalink; EHR: Electronic health records; HES: Hospital Episode Statistics; ICD: International Classification of Disease; OPCS: Office of Population Census Surveys; BNF: British National Formulary
References

1. Persson MSM, Harman KE, Vinogradova Y, Langan SM, Hippisley-Cox J, Thomas KS, Gran S. Incidence, prevalence and mortality of bullous pemphigoid in England 1998-2017: a population-based cohort study. Br J Dermatol. 2021;184(1):68-77. https://doi.org/10.1111/bjd.19022.

2. Kirtschig G, Middleton P, Bennett C, Murrell DF, Wojnarowska F, Khumalo NP. Interventions for bullous pemphigoid. Cochrane Database Syst Rev. 2010:10.

3. British National Formulary (online) London: BMJ Group and Pharmaceutical Press; Available from: https://bnf.nice.org.uk/drug/prednisolone.html. Accessed 25 Jan 2021.

4. Lamberts A, Yale M, Grando SA, Horváth B, Zillikens D, Jonkman F. Unmet needs in pemphigoid diseases: an international survey amongst patients, clinicians and researchers. Acta Derm Venereol. 2019;99(1–2):224–5.

5. Benchimol EI, Smeeth L, Guttmann A, Harron K, Moher D, Petersen I, et al. The REporting of studies conducted using observational routinely-collected health data (RECORD) statement. PLoS Med. 2015;12(10):e1001885.

6. Chisholm J. The read clinical classification. BMJ. 1990;300(6732):1092.

7. Herrett E, Gallagher AM, Bhaskaran K, Forbes H, Mathur R, van Staa T, et al. Data resource profile: clinical practice research datalink (CPRD). Int J Epidemiol. 2015;44(3):827–36.

8. Lewis JD, Biker WB, Weinstein RB, Strom BL. The relationship between time since registration and measured incidence rates in the general practice research database. Pharmacoeconomic Drug Saf. 2005;14(7):443–51.

9. Persson MSM, Harman KE, Vinogradova Y, Langan SM, Hippisley-Cox J, Thomas KS, Gran S. Validation study of bullous pemphigoid and pemphigus vulgaris recording in routinely collected electronic primary healthcare records in England. BMJ Open. 2020;10(7):e035934. https://doi.org/10.1136/bmjopen-2019-035934. PMID: 32665386; PMCID: PMC7365488.

10. Burton J, Harman R, Peachey R, Warin R. Azathioprine plus prednisone in treatment of pemphigoid. Br Med J. 1978;2(6146):1190–1.

11. Sticherling M, Franke A, Auerer E, Glaeser R, Hertl M, Pfeiffer C, et al. An open, multicentre, randomized clinical study in patients with bullous pemphigoid comparing methylprednisolone and azathioprine with methylprednisolone and dapsone. Br J Dermatol. 2017;177(5):1299–305.

12. Kuan V, Denaxas S, Gonzalez-Izquierdo A, Direk K, Bhatti O, Husain S, et al. A chronological map of 308 physical and mental health conditions from 4 million individuals in the English national health service. Lancet Digit Health. 2019;1(2):e63–77.

13. Jain A, Walker JL, Mathur R, Forbes HJ, Langan SM, Smeeth L, van Hoek AJ, Thomas SL. Zoster vaccination inequalities: a population based cohort study using linked data from the UK Clinical Practice Research Datalink. PLoS one. 2018;13(11):e0207183.

14. Statistics OfN. Dataset: Population Estimates for UK, England and Wales, Scotland and Northern Ireland 2017 [Available from: https://www.ons.gov.uk/datasets/mid-year-pop-est/editions/time-series/versions/4.

Publisher’s Note
Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.