

Nonadherence to systemic immune-modifying therapy in people with psoriasis during the COVID-19 pandemic: findings from a global cross-sectional survey

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Abstract

Background Nonadherence to immune-modifying therapy is a complex behaviour which, before the COVID-19 pandemic, was shown to be associated with mental health disorders in people with immune-mediated diseases. The COVID-19 pandemic has led to a rise in the global prevalence of anxiety and depression, and limited data exist on the association between mental health and nonadherence to immune-modifying therapy during the pandemic.

Objectives To assess the extent of and reasons underlying nonadherence to systemic immune-modifying therapy during the COVID-19 pandemic in individuals with psoriasis, and the association between mental health and nonadherence.

Accepted: 17 December 2022

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Methods Online self-report surveys (PsoProtectMe), including validated screens for anxiety and depression, were completed globally during the first year of the pandemic. We assessed the association between anxiety or depression and nonadherence to systemic immune-modifying therapy using binomial logistic regression, adjusting for potential cofounders (age, sex, ethnicity, comorbidity) and country of residence.

Results Of 3980 participants from 77 countries, 1611 (40.5%) were prescribed a systemic immune-modifying therapy. Of these, 408 (25.3%) reported nonadherence during the pandemic, most commonly due to concerns about their immunity. In the unadjusted model, a positive anxiety screen was associated with nonadherence to systemic immune-modifying therapy [odds ratio (OR) 1.37, 95% confidence interval (CI) 1.07–1.76]. Specifically, anxiety was associated with nonadherence to targeted therapy (OR 1.41, 95% CI 1.01–1.96) but not standard systemic therapy (OR 1.16, 95% CI 0.81–1.67). In the adjusted model, although the directions of the effects remained, anxiety was not significantly associated with nonadherence to overall systemic (OR 1.20, 95% CI 0.92–1.56) or targeted (OR 1.33, 95% CI 0.94–1.89) immune-modifying therapy. A positive depression screen was not strongly associated with nonadherence to systemic immune-modifying therapy in the unadjusted (OR 1.22, 95% CI 0.94–1.57) or adjusted models (OR 1.14, 95% CI 0.87–1.49).

Conclusions These data indicate substantial nonadherence to immune-modifying therapy in people with psoriasis during the pandemic, with attenuation of the association with mental health after adjusting for confounders. Future research in larger populations should further explore pandemic-specific drivers of treatment nonadherence. Clear communication of the reassuring findings from population-based research regarding immune-modifying therapy-associated adverse COVID-19 risks to people with psoriasis is essential, to optimize adherence and disease outcomes.

What is already known about this topic?

- Before the COVID-19 pandemic, mental health disorders including anxiety and depression were shown to be associated with nonadherence to immune-modifying therapy in individuals with immune-mediated diseases.
- The COVID-19 pandemic has led to a rise in the global prevalence of mental health disorders in the general population.
- The extent of nonadherence to immune-modifying therapy in individuals with psoriasis and its association with mental health during the COVID-19 pandemic remains poorly understood.

What does this study add?

- One-quarter of individuals with psoriasis who completed PsoProtectMe reported nonadherence to systemic immune-modifying therapy during the pandemic, primarily due to concerns around their immunity.
- After adjusting for confounders (age, sex, ethnicity, comorbidity) and country of residence, the association between a positive screen for anxiety and nonadherence to immune-modifying therapy in individuals with psoriasis was attenuated and no longer significant.
- Future research in larger populations should further explore pandemic-specific drivers of treatment nonadherence.
- Clear communication of the reassuring findings from population-based research regarding immune-modifying therapy-associated adverse COVID-19 risks to individuals with psoriasis is essential, to optimize adherence and disease outcomes.

Treatment adherence refers to the extent to which a person's behaviour in taking medication corresponds with agreed recommendations from a healthcare provider.¹ This is in terms of dosage, timing and frequency of drug administration, and is based on available clinical evidence demonstrating optimal outcomes with minimal side-effects.¹ Nonadherence can be described as either unintentional or intentional.² Unintentional nonadherence occurs when an individual wants to follow their prescribed treatment regimen but is unable to do so due to lack of capacity or specific resources (e.g. forgetfulness or cost of medications).² In contrast, intentional nonadherence occurs when an individual decides not to follow recommendations.² Intentional nonadherence is a complex behaviour influenced by several factors, including perceptual factors that influence their motivation to start and continue treatment (e.g. beliefs and preferences) and mental health.^{3–5} Before the COVID-19 pandemic, an association between mental health conditions such as anxiety or depression and nonadherence was found in a range of long-term conditions,^{3,5} including immune-mediated inflammatory diseases such as psoriasis;⁶ however, it is unclear whether these associations have changed during the pandemic.

The mainstay of treatment for moderate-to-severe psoriasis is systemic immune-modifying therapy, either standard systemic or targeted biologic therapies.⁷ These agents

have been the subject of considerable attention during the COVID-19 pandemic due to their mechanism of action (i.e. immune modulation) and established association with infections.^{8,9} At the beginning of the COVID-19 pandemic, risk mitigation strategies for individuals receiving immune-modifying therapies focused on behaviours to limit exposure to the virus (e.g. shielding) rather than discontinuing treatment, given the importance of ensuring ongoing control of psoriasis,¹⁰ including avoiding demand on healthcare services due to disease flares. Data from registry- and population-based COVID-19 studies^{9,11–16} have supported this approach, with evidence suggesting that risks of adverse outcomes in this group are mainly driven by the same factors as in the general population (e.g. age, sex, ethnicity and comorbid burden).

Emerging research indicates that the COVID-19 pandemic may have negatively impacted adherence to systemic immune-modifying therapies in people with psoriasis,^{17–24} with nonadherence ranging between 1.6%²⁰ and 68.5%²¹ and considerable variation reported across systemic immune-modifying therapy types.²¹ Global mental health has also been adversely affected in the COVID-19 pandemic.^{25–28} Understanding the extent of nonadherence to different systemic immune-modifying therapies, and the potential factors contributing to it, is the first necessary step in helping patients to gain more benefit from their

medication(s). Furthermore, the COVID-19 pandemic provides an important opportunity to better understand the potential complex relationship between mental health and treatment nonadherence.

To address this, we analysed self-report data from the PsoProtectMe international survey, which explores the global impact of the COVID-19 pandemic on individuals with psoriasis and includes validated screens for anxiety (Generalized Anxiety Disorder-2²⁹) and depression (Patient Health Questionnaire-2³⁰). Our specific objectives were:

1 To characterize the extent of, and reasons underlying, self-reported nonadherence to systemic immune-modifying therapy in people with psoriasis during the COVID-19 pandemic.

2 To assess whether an association exists between a positive screen for anxiety or depression and self-reported nonadherence to systemic immune-modifying therapy in people with psoriasis during the COVID-19 pandemic.

Materials and methods

Design, study participants and recruitment strategy

A cross-sectional survey design was employed. The inclusion criterion was any individual reporting a clinician-confirmed diagnosis of psoriasis. There was no age limit (questions could be completed by the individual or on behalf of someone else). Following its launch on 4 May 2020, PsoProtectMe (<https://psoprotectme.org/>; available in nine different languages) was promoted globally via social media, patient organizations and clinical networks (REC reference 20/YH/0135). Data were collected and managed using REDCap (Research Electronic Data Capture) tools licensed to King's College London Division of Health and Social Care Research.³¹

Materials

We defined a minimum sufficient core set of variables within PsoProtectMe with our study group of clinicians, researchers and patient representatives.^{10,32} Treatment adherence was determined by a question which asked whether the participant had stopped or delayed their systemic immune-modifying medication during the COVID-19 pandemic, and the underlying reason(s) for doing so (see <https://psoprotectme.org/> for full questionnaire). All immune-modifying treatments are listed in Table S1; see [Supporting Information](#). If a respondent was on co-therapy (i.e. prescribed more than one standard systemic and/or targeted therapy), their adherence was assessed for each medication separately. If a respondent who was receiving co-therapy was nonadherent to one or more of their medications, they were classified as nonadherent overall. We used the Generalized Anxiety Disorder 2-item (GAD-2)²⁹ and the Patient Health Questionnaire-2 (PHQ-2)³⁰ to screen for anxiety and depression, respectively; scores of ≥ 3 were considered positive.

Statistical analysis

Data were analysed using SPSS (version 27.0 for Windows). Due to the continuously evolving nature of the COVID-19

pandemic, we specifically assessed the extent, reasons for, and potential determinants of systemic immune-modifying therapy nonadherence during the first year of the pandemic (to 16 March 2021), when most global populations were being affected by some form of containment measure.

We used descriptive statistics to summarize the findings; we reported continuous variables using medians and interquartile ranges (IQRs), and categorical/dichotomous variables as numbers and percentages. We used binomial logistic regression to assess associations between positive screens for anxiety or depression and nonadherence to systemic immune-modifying therapy. These models were then adjusted for potential confounders (age, sex, ethnicity and medical comorbidity), as well as country of residence. All underlying assumptions for all statistical tests were met, unless otherwise stated. A *P*-value of ≤ 0.05 was used to demonstrate statistical significance.

Results

Clinical and sociodemographic characteristics of the study population

A total of 3980 individuals with psoriasis completed PsoProtectMe between 4 May 2020 and 16 March 2021, 1611 (40.5%) of whom were receiving systemic immune-modifying therapy. Of those receiving a systemic immune-modifying therapy, 619 (38.4%) were receiving a standard systemic therapy ($n=121$ as co-therapy) and 1113 (69.1%) were receiving a targeted therapy. The median age of respondents who were receiving systemic immune-modifying therapy was 49.0 years (IQR 20.0), with the majority being female ($n=962$, 59.7%), of white ethnicity ($n=1268$, 78.7%) and residing in the UK ($n=960$, 59.6%). Clinical and sociodemographic characteristics of those receiving systemic immune-modifying therapy are summarized in Table 1. Table S1 provides a breakdown of the standard systemic and targeted immune-modifying therapies used by respondents.

Of 1611 individuals who reported receiving systemic immune-modifying therapy for psoriasis, 1573 (97.6%) completed the anxiety (GAD-2) and depression (PHQ-2) screens. Of these, 405 (25.7%) and 379 (24.1%) respondents had a positive screen for anxiety and depression, respectively.

Extent of, and reasons underlying, nonadherence to systemic immune-modifying therapy during the COVID-19 pandemic

A total of 408 (25.3%) respondents reported nonadherence to their systemic immune-modifying therapy. Specifically, 191 (30.9%) and 235 (21.1%) respondents reported nonadherence to their standard systemic and targeted immune-modifying therapy, respectively (Table 1).

Reasons for nonadherence to systemic immune-modifying therapy are presented in Table 2. Concerns about their own immunity ('I didn't want it to affect my immunity') was the most common reason for discontinuation (48.2%), followed by advice from their doctor ['My doctor told me to stop it' (30.7%)], concern about complications (19.1%) and having no medicine supply (15.2%).

Table 1 Clinical and sociodemographic characteristics of PsoProtectMe respondents who were receiving systemic immune-modifying therapy (total $N=1611$), including those receiving standard systemic ($n=619$) and targeted therapy ($n=1113$)

Clinical and sociodemographic characteristics	Total systemic immune-modifying therapy	Standard systemic therapy	Targeted therapy
Median age, years (IQR)	49.0 (20.0)	48.0 (19.0)	49.0 (19.0)
Sex, N (%)			
Male	645 (40.0%)	219 (35.4%)	465 (41.8%)
Female	962 (59.7%)	399 (64.4%)	644 (57.9%)
Prefer not to say	4 (0.2%)	1 (0.1%)	4 (0.3%)
Ethnicity, N (%)			
White (e.g. European)	1268 (78.7%)	464 (74.9%)	889 (79.9%)
Hispanic or Latino	106 (6.6%)	59 (9.5%)	54 (4.8%)
South Asian (e.g. Indian)	66 (4.1%)	32 (5.2%)	42 (3.7%)
Japanese	60 (3.7%)	17 (2.7%)	51 (4.6%)
Prefer not to say	14 (0.9%)	8 (1.3%)	7 (0.6%)
Unknown	5 (0.3%)	4 (0.6%)	2 (0.2%)
Other ^a	92 (5.7%)	35 (5.7%)	68 (6.1%)
Country of residence, N (%)			
UK	960 (59.6%)	370 (59.8%)	651 (58.5%)
Denmark	28 (1.8%)	9 (1.5%)	24 (2.2%)
Spain	27 (1.7%)	11 (1.8%)	18 (1.6%)
Portugal	73 (4.5%)	27 (4.4%)	48 (4.3%)
Japan	62 (3.8%)	16 (2.6%)	54 (4.9%)
Philippines	20 (1.2%)	18 (2.9%)	3 (0.3%)
Australia	23 (1.4%)	5 (0.8%)	19 (1.7%)
Canada	24 (1.5%)	10 (1.6%)	16 (1.4%)
USA	155 (9.6%)	24 (3.9%)	150 (13.5%)
Chile	50 (3.1%)	40 (6.5%)	11 (1.0%)
Argentina	27 (1.7%)	16 (2.6%)	16 (1.4%)
Other ^a	162 (10.1%)	73 (11.8%)	103 (9.3%)
BMI, kg m ⁻² , median (IQR)	27.3 (8.39)	27.2 (8.5)	27.4 (8.4)
Age of psoriasis onset, years, median (IQR) ^b	20.0 (17.0)	20.0 (19.0)	20.0 (17.0)
Psoriasis type ^c , N (%)			
Plaque	1371 (85.1%)	497 (80.3%)	971 (87.2%)
Guttate	310 (19.2%)	138 (22.3%)	195 (17.5%)
Pustular	123 (7.6%)	62 (10.0%)	73 (6.6%)
Erythroderma	47 (2.9%)	16 (2.6%)	35 (3.1%)
Not sure	66 (4.1%)	34 (5.5%)	36 (3.2%)
Other	58 (3.6%)	27 (4.4%)	36 (3.2%)
Comorbidity ^d , N (%)			
Yes	914 (56.7%)	445 (71.9%)	801 (72.0%)
No	876 (54.4%)	194 (31.3%)	350 (31.4%)
Prior COVID-19 diagnosis (as confirmed on a test), N (%)	148 (9.2%)	26 (4.2%)	36 (3.2%)
Nonadherence ^e , N (%)	408 (25.3%)	191 (30.9%)	235 (21.1%)
Positive GAD-2 screen, N (%)	405 (25.7%)	191 (30.9%)	252 (22.6%)
Positive PHQ-2 screen, N (%)	379 (24.1%)	178 (28.8%)	231 (20.8%)

^aSee Table S2 in Supporting Information for 'other' responses. ^bMissing responses for age of psoriasis onset: total immune-modifying therapy $n=20$; standard systemic therapy $n=13$; targeted therapy $n=7$. ^cRespondents could select more than one psoriasis type. ^dRespondents could select more than one comorbidity. ^eStopped or delayed their standard systemic and/or targeted therapy during the COVID-19 pandemic. BMI, body mass index; GAD-2, Generalized Anxiety Disorder 2-item; IQR, interquartile range; PHQ-2, Patient Health Questionnaire-2.

Table 2 Reasons for nonadherence to systemic immune-modifying therapy ($n=388$), including standard systemic ($n=186$) and targeted ($n=220$) therapy

Reason for nonadherence ^a	Total systemic immune-modifying therapy, N (%) ^b	Standard systemic therapy, N (%) ^c	Targeted therapy, N (%) ^d
I didn't want it to affect my immunity	187 (48.2%)	87 (46.8%)	100 (45.5%)
My doctor told me to stop it	119 (30.7%)	57 (30.6%)	62 (28.2%)
I did not have a supply	59 (15.2%)	27 (14.5%)	32 (14.5%)
I was worried about complications	74 (19.1%)	29 (15.6%)	45 (20.5%)
I wanted to focus on COVID	20 (5.2%)	7 (3.8%)	13 (5.9%)
I forgot to take it because I was worried	11 (2.8%)	7 (3.8%)	4 (1.8%)
I forgot to take it because my routine has changed in the pandemic	19 (4.9%)	10 (5.4%)	9 (4.1%)
It was not effective for my psoriasis	37 (9.5%)	20 (10.7%)	17 (7.7%)
Other ^e	87 (22.4%)	34 (18.3%)	53 (24.1%)

^aRespondents could select more than one reason for nonadherence. ^bMissing responses $n=20$. ^cMissing responses $n=5$. ^dMissing responses $n=15$. ^eSee Table S3 in Supporting Information for 'other' reasons for nonadherence.

Relationship between nonadherence to systemic immune-modifying therapy and anxiety or depression

Anxiety

A total of 405 (25.7%) respondents had a positive GAD-2 anxiety screen; 30.1% of those with a positive anxiety screen were nonadherent to systemic immune-modifying therapy, compared with 23.1% of those with a negative screen (data not shown). A positive screen for anxiety was associated with nonadherence to systemic immune-modifying therapy in the unadjusted model [odds ratio (OR) 1.37, 95% confidence interval (CI) 1.07–1.76]. In particular, there was a significant association between anxiety and nonadherence to targeted therapy (OR 1.41, 95% CI 1.01–1.96). Conversely, anxiety was not associated with nonadherence to standard systemic therapy (OR 1.16, 95% CI 0.81–1.67).

After adjustment for potential confounders (age, sex, ethnicity, medical comorbidity) and country of residence, although the direction of the effect remained, the associations were attenuated and anxiety was no longer significantly associated with nonadherence to overall systemic (OR 1.20, 95% CI 0.92–1.56) or targeted (OR 1.33, 95% CI 0.94–1.89) immune-modifying therapy. After removing respondents whose reason for nonadherence was solely their doctor's advice or having no supply, a positive screen for anxiety was also associated with nonadherence to systemic immune-modifying therapy in the unadjusted model (OR 1.34, 95% CI 1.02–1.76), and this association was similarly attenuated and no longer significant after adjustment for confounders (OR 1.20, 95% CI 0.89–1.60).

Depression

A total of 379 (24.1%) respondents had a positive PHQ-2 depression screen; 28.5% of those with a positive depression screen were nonadherent to systemic immune-modifying therapy, compared with 23.5% of those with a negative screen (data not shown). A positive screen for depression was not strongly associated with nonadherence to systemic immune-modifying therapy in unadjusted (OR 1.22, 95% CI 0.94–1.57) or adjusted (OR 1.14, 95% CI 0.87–1.49) logistic regression models. There was also no association between depression and either standard systemic (unadjusted OR 1.07, 95% CI 0.73–1.56; adjusted OR 0.92, 95% CI 0.61–1.37) or targeted (unadjusted OR 1.18, 95% CI 0.83–1.67; adjusted OR 1.20, 95% CI 0.84–1.73) therapy. After removing respondents whose reason for nonadherence was solely their doctor's advice or having no supply, there was similarly no association between depression and nonadherence to systemic immune-modifying therapy (unadjusted OR 1.12, 95% CI 0.84–1.50; adjusted OR 1.03, 95% CI 0.76–1.40).

Discussion

The extent of nonadherence to systemic immune-modifying therapy within our global sample of individuals with psoriasis during the first year of the COVID-19 pandemic is substantial (25.3%). Furthermore, these data indicate that although a positive screen for anxiety was associated with nonadherence in crude analyses, the association was attenuated after adjustment for confounders.

The proportion of individuals with psoriasis reporting nonadherence to systemic immune-modifying therapy is higher than indicated by some studies conducted before the pandemic.^{33,34} For example, in studies by Chan *et al.*³³ and Thorneloe *et al.*,³⁴ 14.2% and 16.4% of study participants were nonadherent, respectively. Immediately following the worldwide spread of COVID-19, concern emerged regarding the safety of immune-modifying medications, specifically in relation to potential increased susceptibility to and/or severity of COVID-19. Biologic drugs targeting tumour necrosis factors interleukin (IL)-12/23, IL-23 and IL-17 can increase individuals' risk of contracting common and opportunistic infections.^{8,9} However, importantly, there is now a growing reassuring evidence base supporting the continuation of systemic immune-modifying therapies during the pandemic. Registry data suggest that biologics do not increase susceptibility to and/or severity of COVID-19.^{8,12,20,23,24,35–38} For example, our registry-based studies^{12,13} and others^{11,14,15} indicated that biologic use was associated with lower risk of COVID-19-related hospitalization compared with nonbiologic systemic therapies, albeit with potentially confounding shielding behaviour differences across treatment groups.¹⁰ Larger-scale population-based research suggests no differences in COVID-19-related death in adults prescribed targeted immune-modifying therapy compared with those on standard systemic therapy.¹⁶ These data have helped to inform international clinical guidance supporting treatment adherence during the pandemic.¹¹

Our findings (both unadjusted and adjusted logistic regression models) indicate that depression was not significantly associated with nonadherence to systemic immune-modifying therapy during the pandemic. In contrast, prior research conducted before the pandemic suggested an association between depression and treatment nonadherence across a range of chronic conditions,^{3,5} including immune-mediated inflammatory diseases.⁶ Pre-pandemic research in psoriasis also indicated that medication nonadherence was linked to feeling anxious about potential drug adverse effects.³⁹ Indeed, in our unadjusted logistic regression model, we identified an association between anxiety and nonadherence to systemic immune-modifying therapy, more specifically targeted therapy. As targeted therapies are a newer treatment compared with standard systemic therapies,⁴⁰ patients may be more concerned about the potential adverse effects of this therapy both during and beyond the COVID-19 pandemic. Because good clinician communication is positively correlated with patient treatment adherence,⁴¹ it is important for clinicians to clearly communicate the findings from population-based research regarding immune-modifying therapy-associated risks to patients, both during and beyond the COVID-19 pandemic.

However, after adjustment for potential confounders, while the direction of the effect remained, the association between anxiety and nonadherence to targeted immune-modifying therapy was attenuated and no longer significant, although wide confidence intervals reflect a lack of precision of the estimate, and replication in larger populations would be of value. The COVID-19 pandemic is a unique period, with major impacts on global mental health in the general population.^{25–28} There may be different drivers of treatment nonadherence during this period compared with pre-pandemic, such as concerns surrounding own

immunity, as suggested in our study and others.^{18–20,22–24} As the COVID-19 pandemic evolves, it is important to understand and address pandemic-specific drivers of treatment nonadherence in psoriasis, to improve medication behaviours and subsequent patient outcomes.

A strength of our study is that we have expanded a limited evidence base on the association between immune-modifying treatment nonadherence and mental health during the COVID-19 pandemic in individuals with psoriasis using our global dataset. However, this study has several limitations; for example, the cross-sectional design precludes any inferences about causality or directionality of associations. The statistical tests employed may have been underpowered, increasing the probability of type II errors, as reflected by the width of the confidence intervals reducing the certainty of the estimates, and do not take into account the duration of nonadherence. Self-report assessments have been shown to underestimate true levels of medication nonadherence⁴² due to reasons such as social desirability bias. Individuals nonadherent to immune-modifying treatment or with low computer literacy may have been disinclined to participate in this online study, potentially introducing ascertainment bias and under-estimating some of our findings. Our study population included self-selecting responders to PsoProtectMe and was dominated by females of white ethnicity residing in the UK, therefore limiting the generalizability of our results. To validate self-reported sociodemographic and clinical characteristics, future research should consider linkage to registry and healthcare records.

In conclusion, we have identified a substantial prevalence of nonadherence to immune-modifying treatment (roughly 25%) during the COVID-19 pandemic in our international sample of individuals with psoriasis, primarily due to concerns surrounding respondents' immunity. As global mental health has been adversely affected in the pandemic,^{25–28} our finding that depression and anxiety were not strongly related to treatment nonadherence is reassuring. Future research should further explore pandemic-specific drivers of treatment nonadherence in larger populations. Communication of the reassuring findings from population-based research regarding immune-modifying therapy-associated adverse COVID-19 risks to individuals with psoriasis is essential, to optimize adherence and disease outcomes.

Acknowledgments

We are grateful to all the patients who have contributed to PsoProtectMe, all professional and patient organizations who supported or promoted PsoProtectMe, and Prof. Lars Iversen, Prof. Nick Reynolds and Prof. Joel Gelfand for their valuable input. We would like to acknowledge the following individuals for help with translating the PsoProtectMe survey: Dr Haleema Alfailakawi, Dr Wisam Alwan, Dr Rosa Andres Ejarque, Dr Ines Barbosa, Ms Carmen Bugarin Diz, Ms Katarzyna Gryś, Dr Mahira Hamdy El Sayed, Mr Tran Hong Truong, Mr Masanori Okuse, Ms Dagmara Samselska, Ms Isabella Tosi and Ms Ya-Hsin Wang. Thank you to the Engine Group UK for their generous creative input and website expertise.

Funding sources

We acknowledge financial support from the Department of Health via the National Institute for Health and Care Research

(NIHR) Biomedical Research Centre based at Guy's and St Thomas' NHS Foundation Trust and King's College London, the NIHR Manchester Biomedical Research Centre and the Psoriasis Association. The views expressed are those of the author(s) and not necessarily those of the NHS, the NIHR, or the Department of Health and Social Care. S.K.M. is funded by a NIHR Advanced Fellowship (NIHR302258). C.E.M.G. is a NIHR Emeritus Senior Investigator and is funded in part by the Medical Research Council (MRC) (MR/101 1808/1). C.E.M.G. and R.B.W. are in part supported by the NIHR Manchester Biomedical Research Centre. S.M.L. is supported by a Wellcome senior research fellowship in clinical science (205039/Z/16/Z); this research was funded in whole or in part by the Wellcome Trust (205039/Z/16/Z). For the purpose of Open Access, the author has applied a CC BY public copyright licence to any Author Accepted Manuscript (AAM) version arising from this submission. S.M.L. is also supported by Health Data Research UK (grant no. LOND1), which is funded by the UK MRC, Engineering and Physical Sciences Research Council, Economic and Social Research Council, Department of Health and Social Care (England), Chief Scientist Office of the Scottish Government Health and Social Care Directorates, Health and Social Care Research and Development Division (Welsh Government), Public Health Agency (Northern Ireland), British Heart Foundation and Wellcome Trust.

Conflict of interests

J.W. has presented talks for Abbott, AbbVie, Bayer, Boehringer Ingelheim, Chiesi, Merck and Roche. K.J.M. reports personal fees from LEO Pharma and Novartis, outside the submitted work. H.M. reports grants from AbbVie, Almirall, Celgene, Dermal Laboratories, Eli Lilly, Janssen, LEO Pharma, T & R Derma and UCB, outside the submitted work. D.U. reports grants from AbbVie, Almirall, Amgen, Celgene, Dermal Laboratories, Eli Lilly, Janssen, LEO Pharma, T & R Derma and UCB, outside the submitted work. L.M. reports personal fees from AbbVie, Celgene, Janssen, LEO Pharma, Novartis and UCB, outside the submitted work. Additional disclosures from L.M. include Almirall, BMS and Lilly. H.B. reports personal fees from AbbVie, Almirall, Biocad, Boehringer-Ingelheim, Janssen, Kyowa Kirin, LEO Pharma, Novartis, Pfizer and UCB, outside the submitted work. F.C. reports consultancy fees from AnaptysBio, grants from Boehringer Ingelheim, outside the submitted work. C.D.I.C. reports personal fees from Boehringer Ingelheim and UCB Pharma; grants from Janssen, Pfizer, Sandoz, Sanofi; grants and personal fees from AbbVie, Novartis, outside the submitted work. P.D.M. reports grants and personal fees from UCB; personal fees from Janssen and Novartis, outside the submitted work. P.G. reports personal fees from AbbVie, Amgen, Eli Lilly, Janssen, Novartis, Pierre Fabre, Sandoz and UCB, outside the submitted work. D.J. reports personal fees and nonfinancial support from AbbVie, Celgene, Janssen-Cilag, Lilly, LEO Pharma, MEDAC and Novartis; and personal fees from Amgen, outside the submitted work. L.P. reports grants and personal fees from AbbVie, Almirall, Amgen, Boehringer Ingelheim, Janssen, Lilly, Novartis and UCB; and personal fees from Bristol Myers Squibb, Fresenius-Kabi, Mylan, Pfizer, Samsung-Bioepis, Sandoz,

