Br J Dermatol 2025; **192**:728–737
https://doi.org/10.1093/bjd/ljae393
Advance access publication date: 15 October 2024

BJD
British Journal of Dermatology
General Dermatology

A personalized and systematically designed adherence intervention improves photoprotection in adults with xeroderma pigmentosum (XP): results of the XPAND randomized controlled trial

Jessica Walburn,[1] Sam Norton,[2] Robert Sarkany,[3] Martha Canfield,[4] Kirby Sainsbury,[5] Paul McCrone,[6] Vera Araújo-Soares,[7] Myfanwy Morgan,[1] Janette Boadu,[8] Lesley Foster,[3] Jakob Heydenreich,[9] Adrian P Mander,[10] Falko F Sniehotta,[11] Hans Christian Wulf[9] and John Weinman[1]

[1]School of Cancer and Pharmaceutical Sciences, Faculty of Life Sciences & Medicine, King's College London, London, UK
The full list of author affiliations is provided in Appendix 1 at the end of this paper.
Correspondence: Jessica Walburn. Email: jessica.walburn@kcl.ac.uk

Linked Article: Kraemer and Tamura *Br J Dermatol* 2025; **192**:572–573.

Abstract

Background Poor adherence to photoprotection in xeroderma pigmentosum (XP) increases morbidity and shortens lifespan due to skin cancers.

Objectives To test a highly personalized intervention (XPAND) to reduce the dose of ultraviolet radiation (UVR) reaching the face in adults with XP, designed using known psychosocial determinants of poor photoprotection.

Methods A two-arm parallel group randomized controlled trial, including patients with suboptimal photoprotection to receive XPAND or a delayed-intervention control arm that received XPAND the following year. XPAND comprises seven 1 : 1 sessions targeting photoprotection barriers (e.g. misconceptions about UVR) supported by personalized text messages, activity sheets and educational materials incorporating behaviour change techniques. The primary outcome, mean daily UVR dose to face across 21 days in June–July 2018, was calculated by combining UVR exposure at the wrist with a face photoprotection activity diary. Secondary outcomes were UVR dose to face across 21 days in August 2018, time spent outside, photoprotective measures used outside, mood, automaticity and confidence to photoprotect. Financial costs and quality-adjusted life years (QALYs) were calculated.

Results Sixteen patients were randomized; 13 provided sufficient data for primary outcome analysis. The XPAND group ($n=8$) had lower mean daily UVR dose to face [0.03 standard error of difference (SED) (SD 0.02)] compared with controls ($n=7$) [0.43 SED (SD 0.17)] (adjusted difference=−0.25, $P<0.001$, Hedge's g=2.21) at the June 2018 assessment. No significant between-group differences were observed in time spent outside, photoprotection outside, mood or confidence. The delayed-intervention control showed improvements in UVR dose to face (adjusted difference=−0.05; Hedge's g=−0.1), time outside (adjusted difference=−69.9; Hedge's g=−0.28) and photoprotection (adjusted difference=−0.23, Hedge's g=0.45) after receiving XPAND (June 2019 assessment). XPAND was associated with lower treatment costs [−£2642; 95% confidence interval (CI) −£8715 to £3873] and fewer QALYs (−0.0141; 95% CI −0.0369 to 0.0028).

Conclusions XPAND was associated with a lower UVR dose to face in patients with XP and was cost-effective.

Lay summary

Xeroderma pigmentosum (XP) is a genetic condition that stops a person's skin from repairing damage from ultraviolet radiation (UVR), and increases the risk of developing skin cancers. The only way to reduce this risk is to protect the skin by staying indoors and using items such as hats, glasses and sunscreen when outside. However, people with XP can find it difficult to protect their skin all the time.

We designed an intervention (called XPAND) to support people with XP to improve photoprotection. This involved seven tailored conversations, using materials (e.g. a magazine), between a patient and a healthcare professional to identify what motivates them to protect their skin, and what makes it harder. We measured the amount of UVR reaching the face (dose to face), before and after XPAND, compared with a group that didn't do the sessions. Our way of measuring was new, using a UVR monitor worn on the wrist and photoprotection recorded in a diary. The XPAND group had lower dose-to-face measurements afterwards than those who did not receive XPAND immediately, suggesting that it could be successful. However, because we were comparing small groups, we cannot be certain that the result was because of XPAND, or whether the group already had lower dose-to-face measurements.

Overall, our findings from the assessment of value for money found that patients undergoing XPAND had lower service costs and similar outcomes to the comparison group.

Accepted: 7 October 2024

What is already known about this topic?

- Xeroderma pigmentosum (XP) is a rare genetic disorder characterized by multiple skin cancers from early childhood.
- Photoprotection against ultraviolet radiation (UVR) is the only way for people with XP to prevent skin and eye cancers.
- We have recently identified the psychosocial determinants of poor photoprotection in XP.
- No intervention has previously been designed or tested to improve photoprotection in people with XP.

What does this study add?

- This study demonstrates that a personalized adherence intervention, designed by systematically mapping change strategies to the determinants of poor photoprotection, improves photoprotection, reducing the dose of UVR reaching the face.
- Photoprotection improves without impairing emotional wellbeing.
- Reducing the time spent outside is as important as improving the photoprotection used when outside.
- Mood, automaticity, confidence and perceived importance of photoprotection are psychological mechanisms that may contribute to improving photoprotective behaviour in patients with XP.

Xeroderma pigmentosum (XP) is a rare recessive disease involving an impaired response to ultraviolet radiation (UVR), which induces DNA damage.[1] This substantially increases the risk of skin and eye cancers resulting in an average life expectancy of 32 years, with 60% of premature deaths resulting from metastatic cutaneous malignancies.[2] Photoprotection from UVR in daylight is the main means of preventing the cancers: staying indoors as much as possible and using protective clothing and broad-spectrum sun-protective factor 50 sunscreen when outside. Most XP skin cancers (80%) are on the face, head and neck, so face protection is critical,[3] ideally achieved by wearing a legionnaire-style cap with a UVR-protective transparent film at the front, or wide-brimmed hat, glasses and face-buff/scarf.[4] We have previously identified that photoprotection of the face is poor in one-third of patients, and that extreme photoprotection restricts daily activities and impairs emotional wellbeing.[5–9]

Following our previous studies,[5–9] we specifically targeted the psychosocial determinants of poor photoprotection for each patient to create a highly personalized intervention to improve photoprotection in adults with XP[10,11] (Enhancing XP Photoprotection Activities – New Directions, XPAND). XPAND was informed by studies of patients without XP but with high risk of skin cancer[12] and with psychological theory,[13–15] and was designed for delivery by healthcare professionals without specialist psychological training.

The rarity of XP (136 known patients with XP in the UK) necessitated a randomized controlled trial (RCT) with a delayed-intervention control group design. Our novel UVR exposure measurement methodology[7] enabled intensive longitudinal data capture and maximized statistical power by the number of observations recorded per patient.[7] The primary objective was to investigate whether the average daily UVR dose to face was reduced after XPAND compared with the control. We assessed whether change persisted across 21 consecutive days 3 months later, measured effects on psychological variables, and investigated the impact of the intervention in the delayed-intervention control group. Cost-utility analysis assessed the cost-effectiveness of incorporating XPAND into routine care.

Materials and methods

Study design

A phase II assessor-blind two-armed parallel group RCT compared participants who received the XPAND intervention in May–June 2018 with a delayed-intervention control group, who then received XPAND a year later; both groups continued to receive their routine care. Intervention and measurement periods were chosen to control for seasonal differences in environmental UVR. Ethical approval was obtained from the West London & GTAC Research Ethics Committee (17/LO/2110), and the trial is registered at: ClinicalTrials.gov (NCT03445052). The trial protocol[16] and a process evaluation[17] are published elsewhere.

Recruitment

Eligible participants (≥ 16 years) were recruited from the National XP Service at Guy's and St Thomas' NHS Foundation Trust. They had previously been identified in formative research[5–7] as having poor photoprotection as follows:

1 Scores of < 20 on the Adherence to Facial Photoprotection questionnaire;[18]
2 Anything other than 'excellent' or 'very good' recorded on the daily UVR protection diary and the Daily Photoprotection Scale;[5]
3 Having 'resistant' or 'integrated' mode of adjustment associated with lower photoprotection.[6]

Exclusion criteria were cognitive impairment, current clinical depression or anxiety, and being unable to speak or understand spoken or written English. Potential participants were sent an invitation letter and informed consent was obtained during a home visit.

Randomization and masking

Participants were randomized 1 : 1 to receive XPAND in 2018 or 2019. The delayed-intervention group acted as

controls for the 2018 analysis of the primary outcome. Equal allocation to both groups employed a random-allocation sequence for all participants, using a computer program with fixed block sizes of four stratified by sunburn phenotype to balance those with a genetic complementation group associated with an exaggerated vs. a normal sunburn response.[19] Related participants were randomized as a cluster to avoid group contamination. Two of the participants were related and therefore we randomized the first participant recruited and then allocated the next to the same intervention group, accounting for these as a cluster where possible in analyses (e.g. random effect). The trial statistician and XP clinical team were blinded to group allocation.

Procedure

Participants completed baseline assessments for 21 days in April 2018 (t0), which were repeated for 21 days in June–July 2018 (t1) after the main XPAND sessions, and after a booster session in August 2018 (t2). Participants completed the daily diary of face photoprotection and rating of psychological factors, and wore the UVR wrist dosimeter (SunSaver 3, Bispebjerg Hospital, Copenhagen, Denmark)[7] continuously from the start of the first assessment period (t0) until the end of the August assessment period (t2). Participants completed additional self-report measures once at the start of each 21-day period and 6 months after XPAND (December 2018, t3). The delayed-intervention control group additionally followed a similar protocol of assessments and measurements at equivalent times in 2019 (t4, t5 and t6). Figure S1 (see Supporting Information) shows the flow diagram of the trial design.

XPAND intervention

XPAND was delivered by one of two psychologists or by a trained research nurse, following a manual. Each patient received a personalized intervention, with content that addressed their photoprotection barriers (e.g. misconceptions about UVR). XPAND comprised seven 1 : 1 sessions, supported by a consumer-styled magazine containing articles incorporating behaviour change techniques (BCTs), personalized text messages, activity sheets and educational materials. Details of XPAND are shown in Figure 1[16] and published elsewhere.[10,11]

Outcomes

Primary outcome: average daily ultraviolet radiation dose to face (standard error of difference) across 21 consecutive days in June–July 2018 (t1)

The UVR dose to face was calculated as the product of the dose of UVR recorded at the wrist by the dosimeter, and the 'protection factor' of the facial photoprotection behaviours recorded in the daily UVR photoprotection diary (Figure S2; see Supporting Information).[7] For time spent outside during the day, participants recorded the face photoprotection used for each 15-min period (wearing a face visor, hat, hoodie worn up, glasses, face scarf or face buff; applying sunscreen or lip block). Methodological details are provided elsewhere.[7,16]

Secondary outcomes

The secondary outcomes are as follows:

1 Average daily UVR dose to face across 21 consecutive days in August 2018 (t2);

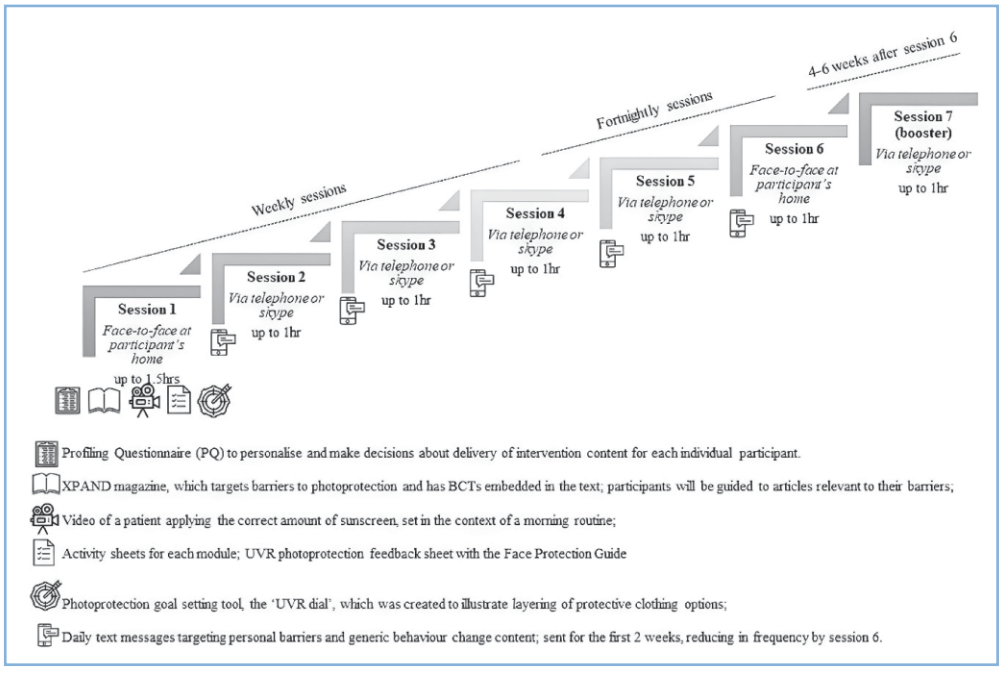

Figure 1 The structure of the XPAND intervention (previously shown as Figure 2 in Walburn *et al.* in *BMJ Open*;[16] used here under Creative Commons CC BY 4.0 license). BCTs, behaviour change techniques; UVR, ultraviolet radiation; XPAND, personalized intervention.

2 Average daily total UVR exposure during t1 and t2;
3 Average daily total time outside during daytime (6am–10pm) (t1 and t2);
4 Average daily total time outside when UVR levels are highest (11am–3pm) (t1 and t2);
5 Average daily proportion of time spent outside during which face photoprotection using clothing was 'very good' or 'excellent' (t1 and t2);
6 Average daily number of times sunscreen was applied irrespective of time outside during each of the 21-day periods (t1 and t2);
7 Average daily measures of psychological factors (single items) rated 0–10 (higher scores are more favourable) (t1 and t2): (a) mood; (b) extent to which photoprotection activities are done without having to think about it consciously (automaticity); (c) self-efficacy to manage barriers to photoprotection ('confidence'); (d) prioritization of photoprotection ('importance').

Tertiary outcomes

Self-report measures were as follows: Health-related quality of life (EQ-5D-5L[20]); Emotional WellBeing (Short-form Warwick–Edinburgh Mental Wellbeing Scale, SWEMWBS[21]) ($\alpha = 0.75$); automaticity of photoprotection activities (four-item subscale: Self-Report Behavioural Automaticity Index, SRBAI[22]) ($\alpha = 0.98$); Self-efficacy to Photoprotect (Photoprotection Self-Efficacy Questionnaire, PhotoSEQ[16]) using clothing ($\alpha = 0.88$) and sunscreen ($\alpha = 0.93$); and Photoprotection Outdoors (Brief Photoprotection Adherence Questionnaire, BPAQ[16]).

Fidelity

A proportion (40%) of the 101 session recordings were evaluated and independent assessors judged whether treatment elements were fully completed, partially completed, or not completed for sessions 1 and 6, and a random selection of follow-up sessions. Interrater agreement assessed by Gwet's agreement coefficients [0.91, 0.76, 0.84, 0.83; 95% confidence interval (CI) 81–85%] was good.

Sample size

A sample size of 10 participants per group with 21 daily observations per participant was required to provide 80% power for a two-sided test of means between groups at 5% significance level to detect a clinically meaningful reduction of 0.10 standard error of difference (SED) per day in UVR dose to face. Recruitment was lower than the target sample size ($n = 16$) but was considered sufficient to continue by the trial steering committee, based on providing 80% power of the study to detect a similar reduction in UVR dose to face of 0.12 SED per day.

Statistical analysis

Data were analysed using Stata version 16.1 statistical software. Daily UVR exposure and daily self-report assessments were analysed, following a modified intention-to-treat framework, using linear mixed-effects models with patients as a random effect to account for repeated observations within individuals. Treatment group and assessment period were included as dummy-coded variables. Group-by-period interaction terms allowed for the estimate of treatment effect to vary across time points. Average daily UVR dose to face during the baseline period, sunburn phenotype, and daily environmental UVR from the nearest Public Health England monitoring station were included as covariates to adjust for baseline differences between groups for these variables. A first-order autoregressive structure was specified to further account for anticipated relation within residuals over time. Given anticipated issues with heteroscedasticity of the residuals, heteroscedasticity robust standard errors were estimated using the Huber–White sandwich estimator. This approach provides standard errors corrected for violation of distribution assumptions (e.g. skew). The days when dosimeter data were not available or diary assessments not reported were not included in the model. Treatment effect estimates are therefore under the assumption that these data are missing at random. Days when the dosimeter was probably not worn but a diary entry completed, indicating that the participant had not gone outside that day, were included in the analysis assuming the SED was 0. Sensitivity analyses for the 'missing at random' assumption for the primary outcome imputed missing days with the mean of the participants' daily assessments across the assessment period.

A similar approach using linear mixed-effects models was used to estimate between-group differences in June–July 2018 and August 2018 for the self-report measures assessed once at the beginning of each period. Due to the number of observations being up to two per participant, no additional residual structure was estimated. Because these analyses were underpowered, no significance testing was applied, and estimates are reported as point estimates with 95% CIs.

Planned exploratory analyses were also undertaken for the delayed-intervention control group by comparing the June–July 2018 and 2019 assessments for this group. Linear mixed-effects models, with a random intercept and autoregressive error structure, were estimated for each outcome including data from all available periods with period included as a dummy-coded variable. The pre-post difference for periods t5 vs. t1, with heteroscedasticity robust standard errors, was estimated as an indicator of treatment effect.

Economic analysis

The economic analyses are indicative of potential cost-effectiveness as the small sample size does not allow for generalizable findings. The cost of the intervention is predominantly therapist time and unit cost of a psychologist. Development costs were not included as it was assumed that these would tend to zero as more patients received the intervention. 'Other service use' was measured using an adapted version of the Client Service Receipt Inventory,[23] which recorded contacts with health and social care services over the 6 months prior to baseline and t3 interviews. Costs were calculated by combining the service use data with unit cost information.[24,25]

Quality-adjusted life years (QALYs) accrued over the period from baseline to t3 were derived from the EQ-5D-5L combined with tariffs. Area under the curve methods were

used assuming a linear change between t0 and t3. Cost and QALY differences between the two groups at t3 were estimated using regression models with baseline cost or EQ-5D-5L score used as an independent variable along with the group identifier. In the case of the intervention having higher costs and producing more QALYs than 'treatment as usual alone', an incremental cost-effectiveness ratio (ICER) was produced, defined as the difference in costs divided by the difference in QALYs.

Results

Recruitment and attrition

Forty-five eligible patients were identified, 37 agreed to be considered, and 16 (43%) consented to participate (Figure 2). Attrition was minimal: one participant from the delayed-intervention group left the study after the baseline assessment. Twelve participants received all seven sessions, two had sessions 6 and 7 combined for logistical reasons, and one had five short sessions. The analysis sample for the primary outcome involved 13 participants due to two faulty dosimeters, providing a total of 492 useable days, across the June and August 2018 reporting periods where dosimetry was available and daily UVR protection diary data was recorded (78% complete, across 630 days expected for 15 people; see Table S1 and Figures S2 and S3; see Supporting Information). The analysis sample consisted of 11 participants providing data across both periods, one providing data only in June, and one providing usable data only in August. Where analyses relied on the diary only, the analysis sample included 15 participants providing a total of 540 useable days (86% complete, across 630 days expected for 15 people).

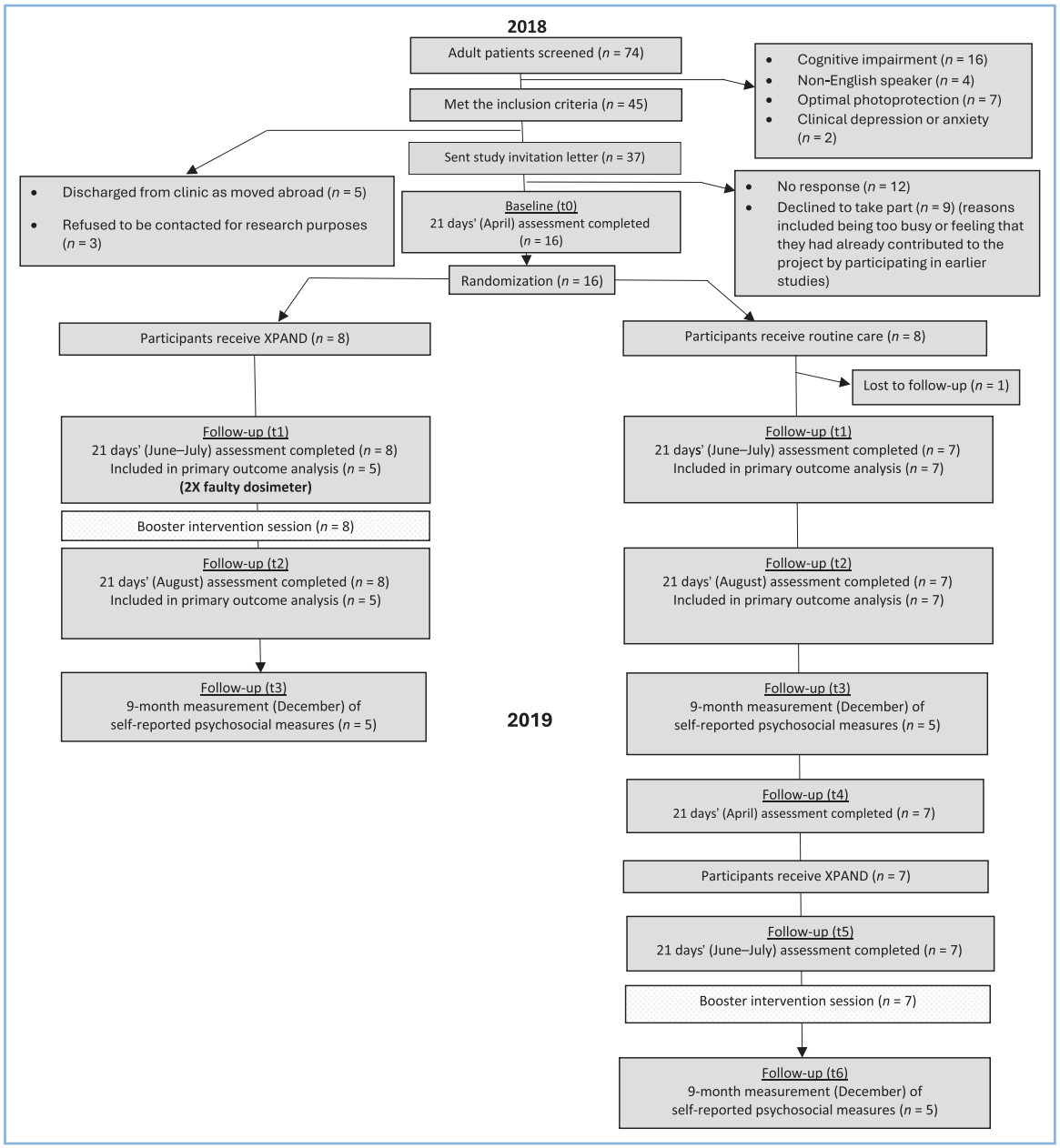

Figure 2 Participant flow through the study.

Table 1 Baseline sample characteristics by treatment group, 2018

	XPAND intervention group ($n=8$)	Delayed-intervention control group ($n=8$)	Total
Demographic factors			
Sex, *n* (%)			
Female	3 (38)	3 (38)	6 (38)
Male	5 (63)	5 (63)	10 (63)
Age, years, mean (SD)	39.9 (15.3)	48.8 (15.9)	44.3 (15.7)
Ethnicity, *n* (%)			
White	5 (63)	5 (63)	10 (63)
Asian[a]	3 (38)	3 (38)	6 (38)
Clinical factors and quality of life			
Age, years, mean (SD)			
Self-reported, at diagnosis	16.1 (17.0)	38.1 (7.4)	27.1 (17.0)
At receipt of lab molecular diagnosis, recorded from the medical notes	36.1 (14.9)	44.5 (15.3)	40.3 (15.2)
Propensity to burn, *n* (%)			
Burner	3 (38)	3 (38)	6 (38)
Nonburner	5 (63)	5 (63)	10 (63)
History of previous cancer, *n* (%)			
Yes	5 (63)	5 (63)	10 (63)
No	3 (38)	3 (38)	6 (38)
XP complementation group, *n* (%)			
A	1 (13)	3 (38)	4 (25)
C	3 (38)	0	3 (19)
E	1 (13)	2 (25)	3 (19)
F	2 (25)	0	2 (13)
V	1 (13)	3 (38)	4 (25)
Quality of life (EQ-5D-5L), mean (SD)	0.9 (0.1)	0.8 (0.1)[b]	0.9 (0.1)

XP, xeroderma pigmentosum. [a]Asian ethnicity includes Pakistani, Bangladeshi, Iranian and Saudi Arabian. [b]Delayed-intervention control, $n=6$.

Baseline demographic and clinical characteristics of the sample by group are shown in Table 1. The patients were predominantly White (63%) and male (63%) with a mean (SD) age of 44.3 (15.7) years. Most participants (63%) belonged to the three XP complementation groups (C, E, V)[19] that do not cause abnormal sunburn responses. Randomization did not achieve good balance between the groups on several key outcome variables at baseline (see Table 2). Those randomized to the intervention group described protection as more automatic, were more confident that they could achieve good protection, and thought protection was more important than those in the delayed-intervention control.

Treatment effect on primary outcome (June–July 2018

As shown in Table 2, the XPAND intervention group had significantly lower mean (SD) daily UVR dose to face [0.03 (0.02)] than the delayed-intervention control group at the June 2018 (primary outcome) post-intervention assessment [0.43 (0.17); adjusted mean difference −0.25 SED, $P<0.001$; large effect size Hedge's g = 2.21]. This difference was maintained at the August 2018 follow-up [intervention: 0.04 (0.03); control: 0.33 (SE 0.20); adjusted difference = −0.20 SED, $P<0.001$; Hedge's g = −1.4].

Treatment effect on secondary outcomes

Total UVR exposure [mean (SD)] was also lower in the intervention group at the June 2018 post-intervention assessment [intervention: 0.07 (0.05); control: 0.58 (0.19); adjusted difference = −0.30 SED, $P<0.001$] and at the August 2018 follow-up [intervention: 0.08 (0.05); control: 0.42 (0.26); adjusted difference = −0.24, $P<0.001$].

Based on 540 daily observations for 15 of 16 randomized patients, there were no significant differences observed for proportion of time spent outside during which face photoprotection was 'very good' or 'excellent', average daily frequency of sunscreen application, confidence in ability to photoprotect, automaticity of photoprotection, perceived importance of photoprotection, or mood. Effect sizes were small, favouring the intervention (Table 2; Figure 3).

Tertiary outcomes

Observed means and estimated mean differences between groups for patient-reported outcomes using standardized scales completed once at the end of each reporting period are shown in Table S2 (see Supporting Information). Differences for quality of life, emotional wellbeing, self-efficacy (confidence) for wearing photoprotective clothing and automaticity were small and nonsignificant. Self-efficacy for applying sunscreen was higher for the intervention group across t1 and t2 (adjusted difference = −0.46, $P<0.05$). Differences for the adherence behaviour subscales were small to medium in favour of the intervention, but only significant for sunscreen application frequency (adjusted difference = −1.25, $P<0.05$).

Exploratory delayed-intervention control group outcomes

We assessed within-person changes in the delayed-intervention control group between the June 2018 and June 2019 assessment periods (Table 2). Although effect

Table 2 Treatment effects on primary outcome and secondary outcomes

		XPAND intervention group		Delayed-intervention control group		Adjusted mean difference			
Variable	**Period**	***n***	**Mean (SD)**	***n***	**Mean (SD)**	**Mean diff (SE)**	***P*-value**	**95% CI**	**Hedge's g**
Daily UVR dose to face (SED)	Apr18[a]	6	0.03 (0.03)	7	0.26 (0.17)				
	Jun18	5	0.03 (0.02)	7	0.43 (0.17)	–0.25 (0.05)[b]	< 0.001	–0.35 to –0.15	–2.21
	Aug18	5	0.04 (0.03)	7	0.33 (0.20)	–0.20 (0.05)[b]	< 0.001	–0.29 to –0.10	–1.40
	Apr19	0		7	0.14 (0.07)				
	Jun19	0		7	0.41 (0.27)	–0.05 (0.08)[c]	0.542	–0.19 to 0.10	–0.12
Daily total (SED)	Apr18	6	0.05 (0.05)	7	0.36 (0.21)				
	Jun18	5	0.07 (0.05)	7	0.58 (0.19)	–0.30 (0.06)[b]	< 0.001	–0.42 to –0.18	–2.01
	Aug18	5	0.08 (0.05)	7	0.42 (0.26)	–0.24 (0.06)[b]	< 0.001	–0.36 to –0.11	–1.20
	Apr19	0		7	0.21 (0.07)				
	Jun19	0		7	0.56 (0.32)	–0.05 (0.09)[c]	0.588	–0.22 to 0.13	–0.10
Daily minutes outside (daylight hours)	Apr18	6	75.95 (42.93)	7	356.43 (163.48)				
	Jun18	5	105.57 (65.83)	7	274.41 (150.86)	–51.11 (81.03)[b]	0.528	–209.92 to 107.70	0.33
	Aug18	5	123.57 (38.28)	7	280.20 (177.17)	–43.52 (73.90)[b]	0.556	–88.36 to 101.31	0.32
	Apr19	0		7	237.65 (124.03)				
	Jun19	0		7	227.65 (131.92)	–69.90 (48.31)[c]	0.148	–164.59 to 24.78	–0.28
Daily high-risk minutes outside (11am–3pm)	Apr18	6	27.26 (15.65)	7	127.52 (68.92)				
	Jun18	5	21.86 (18.84)	7	71.29 (45.18)	–23.80 (23.15)[b]	0.304	–69.18 to 21.58	–0.53
	Aug18	5	41.05 (14.05)	7	87.82 (66.20)	–27.34 (24.54)[b]	0.265	–75.43 to 20.75	–0.54
	Apr19	0		7	76.43 (49.57)				
	Jun19	0		7	68.50 (48.06)	–21.32 (16.26)[c]	0.190	–53.19 to 10.54	–0.20
Daily proportion of time outside photoprotection very good/excellent	Apr18	6	0.68 (0.32)	7	0.29 (0.41)				
	Jun18	6	0.67 (0.38)	7	0.34 (0.35)	0.06 (0.11)[b]	0.546	–0.27 to 0.15	0.11
	Aug18	8	0.68 (0.34)	7	0.34 (0.43)	0.01 (0.10)[b]	0.897	–0.21 to 0.18	0.02
	Apr19	0		7	0.31 (0.44)				
	Jun19	0		7	0.61 (0.37)	0.23 (0.13)[c]	0.065	–0.01 to 0.48	0.45
Daily number times sunscreen applied	Apr18	6	1.03 (0.51)	7	1.32 (0.37)				
	Jun18	7	0.98 (0.65)	7	1.40 (0.56)	–0.33 (0.27)[b]	0.213	–0.86 to 0.19	–0.34
	Aug18	8	1.04 (0.62)	7	1.24 (0.24)	–0.18 (0.21)[b]	0.389	–0.59 to 0.23	–0.23
	Apr19	0		7	1.04 (0.46)				
	Jun19	0		7	1.66 (0.54)	0.27 (0.20)[c]	0.161	–0.11 to 0.66	0.28
Mood	Apr18	6	7.81 (0.89)	7	6.77 (1.47)				
	Jun18	7	8.47 (1.47)	7	7.23 (1.40)	0.20 (0.49)[b]	0.686	–0.77 to 1.17	0.09
	Aug18	8	8.38 (1.50)	7	7.38 (1.33)	0.01 (0.56)[b]	0.984	–1.09 to 1.11	0.00
	Apr19	0		7	6.88 (1.78)				
	Jun19	0		7	8.23 (1.21)	0.80 (0.28)[c]	0.005	0.25 to 1.35	0.40
Automaticity of protection	Apr18	6	8.29 (1.36)	7	6.30 (1.97)				
	Jun18	7	8.07 (2.62)	7	6.86 (2.01)	–0.93 (0.95)[b]	0.329	–2.79 to 0.94	–0.24
	Aug18	8	7.51 (3.28)	7	7.18 (1.89)	–1.71 (1.13)[b]	0.130	–3.94 to 0.51	–0.38
	Apr19	0		7	6.51 (2.60)				
	Jun19	0		7	7.88 (1.58)	0.55 (0.18)[c]	0.003	0.19–0.90	0.21
Confidence in protection	Apr18	6	7.21 (3.07)	7	6.21 (1.83)				
	Jun18	7	8.36 (1.93)	7	6.86 (1.95)	0.76 (0.56)[b]	0.175	–0.34 to 1.86	0.25
	Aug18	8	8.11 (2.19)	7	7.21 (1.81)	0.12 (0.47)[b]	0.790	–0.80 to 1.04	0.04
	Apr19	0		7	6.42 (2.43)				
	Jun19	0		7	7.99 (1.29)	0.58 (0.28)[c]	0.041	0.02–1.13	0.23
Importance of protection	Apr18	6	9.06 (0.77)	7	6.88 (1.87)				
	Jun18	7	8.82 (1.64)	7	7.11 (1.87)	–0.24 (0.69)[b]	0.727	–1.59 to 1.11	–0.09
	Aug18	8	8.60 (1.80)	7	7.40 (1.71)	–0.65 (0.77)[b]	0.395	–2.15 to 0.85	–0.23
	Apr19	0		7	6.57 (2.52)				
	Jun19	0		7	8.27 (1.42)	0.78 (0.28)[c]	0.006	0.22–1.33	0.32

CI, confidence interval; SED, standard error of difference; UVR, ultraviolet radiation. [a]These observations are prior to the group receiving the XPAND intervention. [b]Difference is adjusted mean difference between XPAND group and delayed-intervention control group at the same time point. [c]Difference is adjusted mean difference for delayed-intervention control compared with the same time period in previous year.

sizes favoured the intervention, no statistically significant differences were observed for the mean daily UVR dose to face (adjusted difference = –0.05, Hedge's g = –0.1), total UVR exposure (adjusted difference = –0.05, Hedge's g = –0.10), time outside (adjusted difference = –69.9, Hedge's g = –0.28), proportion of time outside with 'very good' or 'excellent' facial photoprotection (adjusted difference = 0.23, Hedge's g = 0.45), or the number of times sunscreen was applied (adjusted difference = 0.27, Hedge's g = 0.28). Statistically significant differences were observed in favour of the intervention for daily self-reported ratings of mood (adjusted difference = 0.80, Hedge's g = 0.4), automaticity (adjusted difference = 0.55, Hedge's g = 0.21), confidence (adjusted difference = 0.58, Hedge's g = 0.23), and importance of photoprotection (adjusted difference = 0.78, Hedge's g = 0.32).

Treatment effects were consistent with the intention-to-treat sample, in sensitivity analyses which excluded cases without dosimetry/diary data/fewer sessions. No trial-related adverse events were recorded.

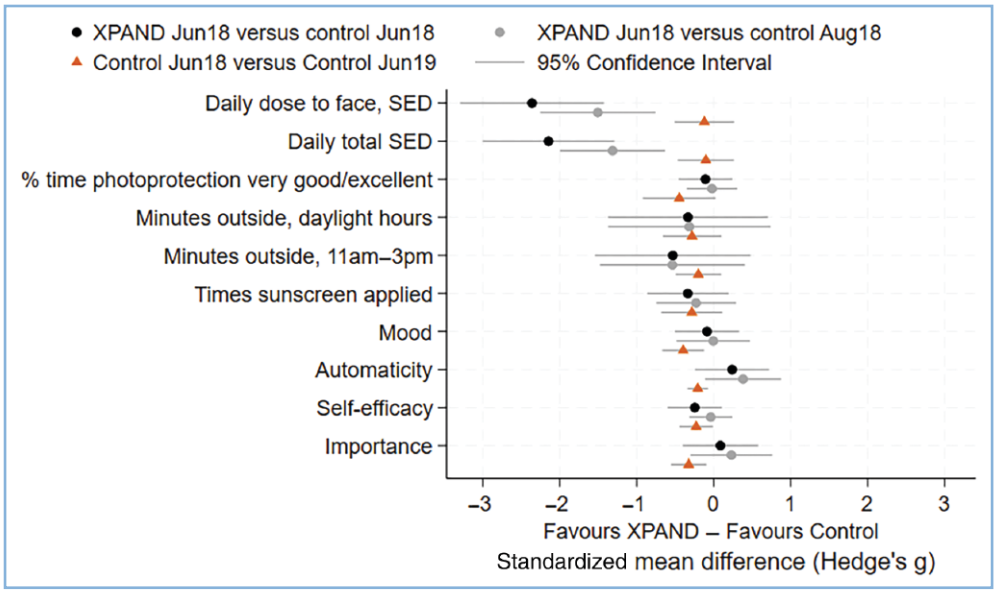

Figure 3 Adjusted mean daily dose to face (standard error of difference, SED) for the primary outcome at assessment t1 and t2, with 95% confidence interval.

Fidelity

Facilitator adherence to the XPAND intervention was high, with an average of 85% treatment fidelity achieved across the six sessions [1: 92% (95% CI 90–94%); 2–5: 78% (95% CI 73–83%); 6: 86% (95% CI 83–90%)].

Economic analysis

Resource use information was collected 9 months after baseline assessment for both XPAND intervention and delayed-intervention control groups. Full details of resource use are provided in Table S3 (see Supporting Information). After adjusting for baseline costs, the intervention group had costs that were on average £2642 lower than for 'treatment as usual' alone (95% CI −£8715 to £3873). The intervention group accrued on average 0.714 QALYs over the period from baseline to t3 compared with 0.699 for the control group. After adjusting for baseline quality of life, the intervention group accrued 0.0141 fewer QALYs (95% CI −0.0369 to 0.0028). The ICER was £187 376 for treatment as usual compared with the intervention. Over a 15-year period it was estimated that the intervention would result in fewer cases of cancer.

Discussion

Participants who received XPAND had a significantly lower UVR dose to face compared with controls. The size of the effect was large, which would be expected to reduce morbidity and mortality from facial skin cancers. The small sample prevented full mediational analysis, and there were no differences between groups on daily measures of psychological process variables, but the results suggest that perceptions of importance of photoprotection, self-efficacy to photoprotect, and automaticity are potential mechanisms of change underlying improvements in photoprotection behaviour. Receipt of XPAND had a positive impact on UVR dose to face without diminishing emotional wellbeing.

The economic evaluation showed that health-related quality of life and hence QALYs were similar between the two groups, although slightly lower in the intervention group. Costs were much lower in the intervention group; however, neither difference was statistically significant. Based on the difference in mean costs and QALYs (adjusted for baseline), we conclude that the intervention was the most cost-effective option.

There are strengths and limitations. The XPAND intervention was based on formative research, which identified the psychological drivers of photoprotection specific to the XP population[4] and then systematically mapped evidenced-based BCTs to these drivers.[10] The primary limitation of the study was the small sample and the failure of randomization to balance baseline differences in dose to face between groups. Although statistical analysis adjusted for baseline levels, we could not ascertain the true effect size. Failure of randomization in small samples is a known pitfall of rare disease trial design.[26] The delayed-intervention control arm aided interpretation of the between-groups findings and increased confidence that XPAND was effective.

In terms of future research, we recommend that XPAND is trialled in a larger international group of patients with XP, with an extended duration of follow-up. High adherence rates suggest that the daily measures are acceptable to participants, consistent with findings in other patient groups.[27,28] UVR dose-to-face measurements highlighted how UVR protection requires a reduction in the *quantity* of exposure alongside better photoprotection *during* exposure. We consider that an adapted version of XPAND may be a promising new approach to improving photoprotection in the many patients who do not have XP but are also at high risk of skin cancer.[29] Despite extensive efforts, poor photoprotection has proven hard to improve in patients with melanoma and nonmelanoma skin cancer.[30,31]

Despite the challenges of evaluating an intervention in an extremely rare disease, our findings show that receipt of XPAND was associated with a lower UVR dose to face, and exploratory analysis pointed to the psychological mechanisms responsible. The intervention was cost-effective and did not impair emotional wellbeing, thus justifying service implementation.

Acknowledgements

We thank Public Health England for providing access to environmental ultraviolet radiation (UVR) data from their solar network monitoring stations. We also thank Lucy Hardy, Martha Hogg, Megan O'Neill, Amanda Pickering, India Punjabi and Raya Vinogradov for conducting the fidelity checks. Many thanks to Federica Picariello for supporting the data analysis. Many thanks to Alice Sarkany, Martin Nemec and Whitney Scott for entering data from the UVR daily diaries. We would like to acknowledge valuable support of the XP national clinical team (Hiva Fassihi, Isabel Garrood, Tanya Henshaw, Alan Lehmann, Sally Turner) and the PPI panel (Cathy Coleman, Ben Fowler, Ros Tobin, Sandra Webb). We are indebted to the participants for giving up their time to receive XPAND, as well as completing the daily diaries and wearing the dosimeters.

Funding sources

This study/project was funded by the National Institute for Health and Care Research (NIHR) [Programme Grants for Applied Research (RP-PG-1212 20009)]. The views expressed are those of the author(s) and not necessarily those of the NIHR or the Department of Health and Social Care.

Conflicts of interest

None to declare.

Data availability

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

Ethics statement

This research has been approved by the West London & GTAC Research Ethics Committee (17/LO/2110).

Patient consent

Written patient consent for publication was obtained.

Supporting Information

Additional Supporting Information may be found in the online version of this article at the publisher's website.

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Appendix 1: Full list of author affiliations

[1]School of Cancer and Pharmaceutical Sciences, Faculty of Life Sciences & Medicine, King's College London, London, UK
[2]Psychology Department, Institute of Psychiatry, Psychology and Neuroscience, King's College London, London, UK
[3]National Xeroderma Pigmentosum Service, Guy's and St Thomas' NHS Foundation Trust, London, UK
[4]Health Psychology Section, Institute of Psychiatry, Psychology and Neuroscience, King's College London, London, UK
[5]Population Health Institute, Faculty of Medical Sciences, Newcastle University, Newcastle upon Tyne, UK
[6]Institute for Lifecourse Development, Faculty of Education, University of Greenwich, London, UK
[7]Centre for Preventive Medicine and Digital Health (CPD), Division of Prevention, Medical Faculty Mannheim, Heidelberg University, Mannheim, Germany
[8]Health Service & Population Research Department, Institute of Psychiatry, Psychology & Neuroscience, King's College London, London, UK
[9]Department of Dermatology, Frederiksberg and Bispebjerg Hospitals, University of Copenhagen, Copenhagen, Denmark
[10]Centre for Trials Research, Cardiff University, Cardiff, UK
[11]Center for Preventive Medicine and Digital Health (CPD), Division of Public Health, Social and Preventive Medicine, Medical Faculty Mannheim, Heidelberg University, Mannheim, Germany