Drug Safety (2020) 43:1011–1022
https://doi.org/10.1007/s40264-020-00959-8

ORIGINAL RESEARCH ARTICLE

The Effect of Positively Framing Side-Effect Risk in Two Different Formats on Side-Effect Expectations, Informed Consent and Credibility: A Randomised Trial of 16- to 75-Year-Olds in England

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Published online: 16 June 2020
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Abstract

Introduction Reframing side-effect information in patient information leaflets (PILs) in terms of those who remain side-effect–free may reduce negative expectations and side-effects, although there are concerns this may impact informed consent. This study compared two versions of positively framed PILs with current practice to see which reduces side-effect expectations whilst maintaining informed consent and credibility.

Methods We commissioned Ipsos MORI to conduct an online survey of 16- to 75-year-olds in England. 1067 people completed the study and were randomised to receive a PIL for a hypothetical new antibiotic that either communicated side-effects following current practice ($n = 356$), used positive framing with natural frequencies ($n = 356$), or positive framing with percentages ($n = 355$). After reading the leaflet, participants completed measures of their side-effect expectations, absolute risk perceptions, and satisfaction and credibility of the leaflet.

Results Both positively framed PILs resulted in significantly lower side-effect expectations compared with the current PIL for all side-effects ($ps < 0.001$), apart from seizure. Pairwise comparisons showed no difference in side-effect expectations between the two positively framed PILs ($ps > 0.626$). The positively framed PIL using natural frequencies produced more accurate risk perceptions than the same leaflet using percentages; but performed equally to the current PIL. There was no difference between the leaflets in terms of satisfaction with or credibility of the PILs.

Conclusion Positively framed PILs using natural frequencies significantly reduced side-effect expectations and provided the most accurate risk perceptions without impacting satisfaction or credibility. Replication is needed with patients prescribed new medication and those with lower educational status.

1 Introduction

It is widely acknowledged that medications may generate adverse effects. Around 6.5% of hospital admissions are related to these adverse effects [1]. As such, adverse effects (or side-effects as we will refer to them following the terminology used in patient information leaflets) can be a great cause for concern to patients, reducing their quality of life and wellbeing, as well as influencing their adherence and therefore the therapeutic benefit of the medication [2–4]. As a result, side-effects can cost health services (such as the National Health Service in the United Kingdom) billions in additional healthcare costs due to GP and A&E visits, additional prescriptions to combat side-effects and unused medication [5].

Not all side-effects are related to the pharmacological action of medications [6, 7]. Many consist of nonspecific symptoms that are attributed to the medication [8]. These nonspecific side-effects can arise through a psychological phenomenon known as the nocebo effect in which these noxious symptoms are largely generated through negative expectations [9], for example, after reading accompanying patient information leaflets (PILs) containing a detailed and lengthy list of possible side-effects.

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s40264-020-00959-8) contains supplementary material, which is available to authorized users.

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Key Points

Positively framing patient information leaflets (PILs) using natural frequencies reduces side-effect expectations with no seeming repercussions on satisfaction, credibility of the PIL or informed consent.

Policy makers should consider how side-effect risk is framed in PILs, but first replication is needed in a clinical sample and in those with lower educational status.

Consideration also needs to be given to the verbal risk descriptors used in positively framed PILs.

If we can reduce the occurrence of nocebo effects, we could therefore reduce the experience of side-effects. There is rife debate in the literature about the effectiveness (and ethics) of withholding side-effect information to reduce expectations and therefore nocebo-induced side-effects [10]. Although this might reduce side-effects, it does not follow the ruling of the UK Supreme Court that doctors should not 'cherry pick' the risk information given to patients [11]. One potential resolution is the use of positive framing [12, 13].

The framing effect reflects a type of cognitive bias, where people respond differently to a described probability depending on how it is portrayed [e.g. as a loss (negative) or as a gain (positive)] [14], and has been shown to influence therapy preference [15] and health-related behaviours [16]. According to current guidelines, medication side-effect information is communicated in PILs with side-effects listed in the order of their commonality, explaining the number of people who will be affected (e.g. "Common, may affect up to 1 in 10 people") [17]. However, this leads to gross overestimation of side-effect risk in the general public as people interpret 'common' as meaning more than chance (i.e. > 5 in 10), which is in conflict with the numerical descriptor; as such it has been found that combined descriptors can lead to a relative overestimation of risk of up to 800% [18–20]. Reframing side-effects positively, to communicate the number of people who will remain side-effect free, is an example of libertarian paternalism [21], in which 'nudge' techniques can guide people's choices so that outcomes improve, without withholding any information that would therefore impact informed consent or patient autonomy. Positive framing could therefore not only reduce non-adherence through reducing the nocebo effect but also reduce intentional non-adherence whereby people are put off by long lists of side-effects and decide not to take the medication [22].

Positively framing side-effect risk in PILs significantly reduces side-effect occurrence in healthy volunteers taking a sham medicine compared with current practice [23] and without altering their perceptions of the trustworthiness of the information. However, positively framed side-effect risk information can be presented in various ways [13]. These include verbal descriptors, natural frequencies and percentages, which may influence side-effect risk perception to varying degrees [24]. In addition there is concern that positive framing may reduce patients' side-effect expectations and absolute risk perceptions to the extent that informed consent is no longer upheld [13].

There is a need to identify the optimal method of presenting positively framed side-effect information, to test which best helps readers to form accurate side-effect expectations and estimates of absolute risk while also maintaining the reader's trust and informed consent.

1.1 Research Objectives

The aim of this study was to identify the optimal method of presenting positively framed side-effect information by exploring the effect of information about side-effects that consists of combined verbal and natural frequency information, or verbal and percentage information, versus current practice. Outcomes consisted of participants'.

1. Side-effect expectations,
2. Perceived absolute risk of side-effects,
3. Satisfaction with the PIL information,
4. Perceived PIL credibility.

2 Method

2.1 Design

The market research company Ipsos MORI were commissioned to conduct an online survey of 16- to 75-year-olds living in England. Data collection commenced on 28 October and was completed on 7 November 2019. This study was approved by the Research Ethics Committee at King's College London (reference MRA-19/20-14325).

The survey incorporated a randomised controlled trial design with participants randomised to read one of three PILs and answer questions about them.

2.2 Participants

Participants were recruited from Ipsos MORI's panel of people who had signed up to take part in internet surveys (approximately $n = 160{,}000$). Due to concerns that older adults on internet survey panels are not representative of the general population, we excluded those aged over 75 years [25, 26].

2.3 Sample Size

To ensure a demographically representative sample, Ipsos MORI used quotas based on participant age and gender (interlocked), location, and working status according to data from the Publishers Audience Measurement Company Ltd [27]. A sample size target of 1067 participants was set to provide a sample error of plus or minus 3% at the total sample level.

2.4 Procedure

Those who met the inclusion criteria on the survey panel were emailed a link to the survey. After providing informed consent, participants completed baseline questions and then were allocated to read one of three different PILs for a hypothetical new antibiotic, Ormicillin. This was decided by an algorithm in the survey software which allocated participants to the condition that had the lowest number of completed responses at that time. After reading their assigned leaflet, participants were asked about their side-effect expectations, absolute side-effect risk perceptions, and satisfaction and credibility of information in the PIL. After completing the survey participants received 100 'credits' (equivalent to £1).

To ensure participant attention in the survey, we had a range of checks in place. Firstly, based on the average reading speed and the ability of people to effectively speed read [28], we used a time monitor once participants had reached the PIL so that those who clicked forward to the next question in less than one minute were automatically screened out of the survey. Secondly, we had three attention check questions after the leaflet (e.g. taking this medication should not affect your ability to drive or operate machinery—true/false), and participants who got any of these questions wrong were also screened out.

2.5 Materials

2.5.1 Demographic Characteristics

Participants were asked demographic questions concerning their age, gender, ethnicity, highest level of education, employment status and health.

2.5.2 Patient Information Leaflets (PILs)

The three leaflets contained identical information (apart from the side-effect section), and were based on a current leaflet in use for penicillin [29]. The control leaflet used the current recommended practice for communicating side-effect information (e.g. Common, up to 1 in 10 people are affected), the positively framed natural frequency leaflet used positive side-effect framing with natural frequency descriptors (e.g. Uncommon, 9 in 10 people are not affected), and the positively framed percentage leaflet used positive framing with percentage descriptors (Uncommon, 90% of people are not affected). See Table 1 for differences in side-effect section between the three PILs, and the electronic supplementary material for a full copy of PILs.

2.5.3 Side-Effect Expectations

One side-effect from each of the risk descriptor groups was selected and participants were asked how likely they would be to experience that side-effect if they took Ormicillin from a scale of 1 (very unlikely) to 5 (very likely). These side-effects were diarrhoea, nausea, dizziness, anaemia and seizure. In addition, they were asked their expectations of experiencing ANY side-effect.

2.5.4 Absolute Side-Effect Risk Perceptions

To provide an indicator of patients' ability to provide informed consent for medication, it has been suggested to measure absolute risk perceptions [13]. This provides evidence of patients' understanding of a certain event happening, in this case side-effects. As such, for the same side-effects asked about with regards to their personal side-effect expectations (diarrhoea, nausea, dizziness, anaemia, seizure and ANY side-effect) participants were asked to estimate how many out of 10,000 people who take Ormicillin would develop these side-effects.

2.5.5 Satisfaction

Seven statements about the clarity of the information, the type of information provided, and overall satisfaction with the PIL were presented and rated from 1 (strongly disagree) to 5 (strongly agree).

2.5.6 Credibility

Using the Myers credibility index [30], participants rated the PIL from 1 to 5 on five continuums: trust, accuracy, fairness, disclosure and bias.

2.6 Analysis

Due to non-normal distribution, Kruskal–Wallis tests were carried out to assess differences in the mean ranks for side-effect expectations, and satisfaction and credibility ratings of the PIL between the three conditions, and Dunn's test was used to carry out post-hoc pairwise comparisons for significant results, adjusting for multiple testing using the Bonferroni correction. Each side-effect and item in the satisfaction and credibility ratings were analysed separately.

Table 1 Side-effect section in each of the three PILs

Current PIL	Positive frame—natural frequencies	Positive frame—percentages
Very common (more than 1 in 10 people are affected) Stomach pain Diarrhoea	**Uncommon** (8 in 10 people are **not** affected) Stomach pain Diarrhoea	**Uncommon** (80% of people are **not** affected) Stomach pain Diarrhoea
Common (up to 1 in 10 people are affected) Nausea Vomiting Black 'hairy' tongue Chills or fever Severe skin rash, itching or peeling	**Very uncommon** (9 in 10 people are **not** affected) Nausea Vomiting Black 'hairy' tongue Chills or fever Severe skin rash, itching or peeling	**Very uncommon** (90% of people are **not** affected) Nausea Vomiting Black "hairy" tongue Chills or fever Severe skin rash, itching or peeling
Uncommon (up to 1 in 100 people are affected) Difficulty breathing Dizziness Swelling of the face or throat Pain and swelling of the joints (arthritis)	**Rare** (99 in 100 people are **not** affected) Difficulty breathing Dizziness Swelling of the face or throat Pain and swelling of the joints (arthritis)	**Rare** (99% of people are **not** affected) Difficulty breathing Dizziness Swelling of the face or throat Pain and swelling of the joints (arthritis)
Rare (up to 1 in 1000 people are affected) Various forms of anaemia (reduction in red blood cells) causing pale skin, or weakness Other blood disorders causing excessive bleeding (including blood in your urine or stools), bruising, sore throat, or general illness	**Very rare** (999 in 1000 people are **not** affected) Various forms of anaemia (reduction in red blood cells) causing pale skin, or weakness Other blood disorders causing excessive bleeding (including blood in your urine or stools), bruising, sore throat, or general illness	**Very rare** (99.9% of people are **not** affected) Various forms of anaemia (reduction in red blood cells) causing pale skin, or weakness Other blood disorders causing excessive bleeding (including blood in your urine or stools), bruising, sore throat, or general illness
Very rare (up to 1 in 10,000 people are affected) Kidney problems Seizures (fits)	**Extremely rare** (9999 in 10,000 people are **not** affected) Kidney problems Seizures (fits)	**Extremely rare** (99.99% of people are **not** affected) Kidney problems Seizures (fits)

As 'more than 1 in 10′ does not lend itself to positive framing, the positively framed PILs gave an exact probability

PIL patient information leaflet

For absolute side-effect risk perception, responses were collapsed into correct versus incorrect estimates based on the corresponding statistical risk descriptors (e.g. 1 in 10, 1 in 100, etc.) to see which PIL produced the most correct estimates, and differences in distributions were analysed using chi-square. Post-hoc pairwise comparisons were carried out for significant results using chi-square, adjusting for multiple testing using the Bonferroni correction.

For all analyses, answers of 'prefer not to say' were excluded. See the electronic supplementary material for a copy of the full questionnaire and topline results.

3 Results

3.1 Participant Characteristics

A total of 1067 participants completed the study and were included in the final sample (see Fig. 1 for participant flow). Demographic characteristics of the sample are given in Table 2. There was no difference in the demographics between the three groups ($p > 0.05$).

3.2 Side-Effect Expectations

The distribution of side-effect expectations for each of the side-effects asked about are shown in Table 3. Both positively framed PILs resulted in a higher proportion of 'unlikely/very unlikely' responses for all side-effects asked about, but the difference was more pronounced for the more common side-effects in the PIL, that is, diarrhoea, nausea and dizziness. Both positively framed PILs resulted in similar response distributions. There was no difference in the distribution of 'don't know' responses between the three different PIL conditions, apart from the item 'any side-effect'.

Median rankings of side-effect expectations were significantly different across all PILs for each of the side-effects (see Table 4). Adjusting for multiple testing, pairwise comparisons showed that positively framed PILs using natural frequencies and percentages resulted in significantly lower side-effect expectations compared with the current PIL for all side-effects ($ps < 0.001$), apart from seizure in which only the positively framed PIL using percentages resulted in significantly lower expectations ($p = 0.008$). Pairwise

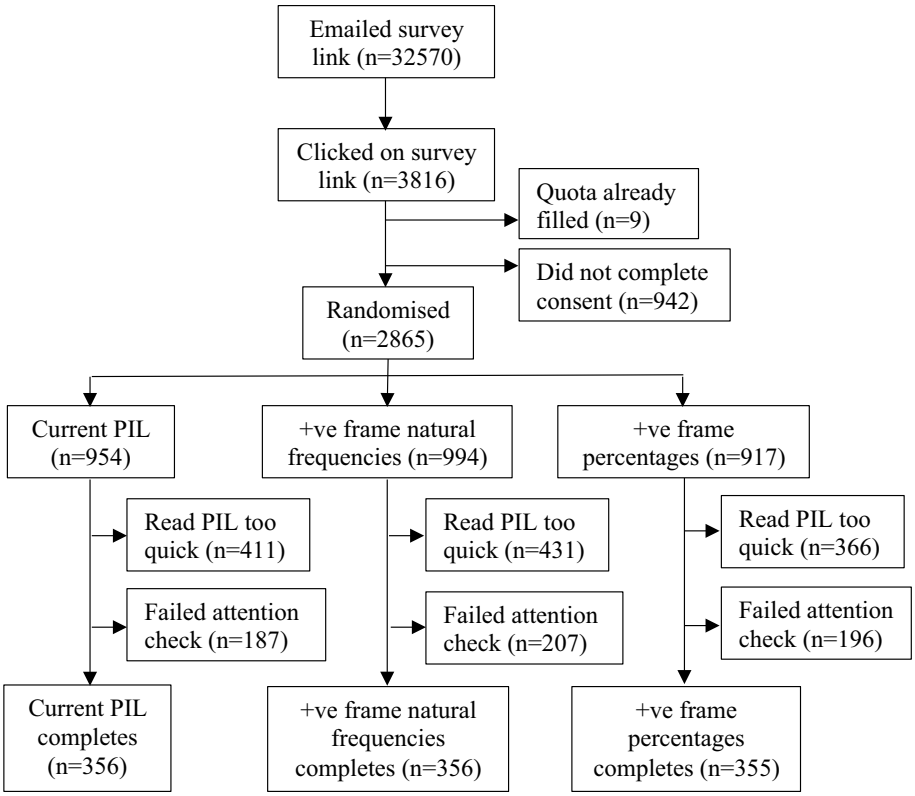

Fig. 1 Participant flow through the study. *PIL* patient information leaflet, *+ve* positive

comparisons showed no significant difference in side-effect expectations between the two positively framed PILs ($ps > 0.626$).

3.3 Absolute Risk Perceptions

The three PILs resulted in significantly different proportions of correct and incorrect absolute risk perceptions, apart from the side-effect 'dizziness' (see Table 5). Multiple comparisons showed that the positively framed PIL using natural frequencies overall outperformed the positively framed PIL using percentages; producing equally correct responses for diarrhoea and nausea ($ps > 0.999$), but more correct responses for anaemia and seizure ($p < 0.001$), while the PIL using percentages produced more correct responses for any side-effects ($p = 0.033$).

Comparing the positively framed PIL using natural frequencies and the current PIL, multiple comparisons showed they performed equally, with no difference in the proportion of correct responses for any side-effect, anaemia and seizure ($ps > 0.87$), with the current PIL only providing more correct responses for nausea ($p = 0.042$), and the positively framed PIL using natural frequencies only providing more correct responses for diarrhoea ($p < 0.001$).

3.4 Satisfaction and Credibility of the PIL

There was no significant difference between the leaflets in terms of satisfaction with or credibility of the PILs (see Table 6). All three leaflets scored well for both outcomes.

4 Discussion

This study looked at two different ways of presenting positively framed side-effect information compared with current practice, to test which best helps readers to form accurate side-effect expectations and estimates of absolute risk while also maintaining the reader's trust and enabling informed consent. We found that both forms of positive framing significantly reduced side-effect expectations for all side-effects asked about at varying risk levels. The reduction in side-effect expectations was more pronounced for the more common side-effects such as diarrhoea and nausea, which is unsurprising as these generate the highest side-effect expectations under current PIL formats [19]. There was no difference in side-effect expectations between the two types of positively framed leaflet.

Despite concerns that positive framing may reduce side-effect expectations to the point that informed consent

Table 2 Demographic characteristics of the sample

Characteristics	Current PIL ($n=356$)	Positive frame natural frequencies ($n=356$)	Positive frame percentages ($n=355$)	Total ($N=1067$)
Gender				
Male	172 (48.3)	179 (50.3)	170 (47.9)	521 (48.8)
Female	184 (51.7)	177 (49.7)	185 (52.1)	546 (51.2)
Age, *n* (%)				
16–24 y	50 (14.0)	50 (14.0)	52 (14.6)	152 (14.2)
25–34 y	67 (18.8)	66 (18.5)	66 (18.6)	199 (18.7)
35–44 y	61 (17.1)	62 (17.4)	61 (17.2)	184 (17.2)
45–54 y	67 (18.8)	66 (18.5)	67 (18.9)	200 (18.7)
55–64 y	58 (16.3)	59 (16.6)	56 (15.8)	173 (16.2)
65–75 y	53 (14.9)	53 (14.9)	53 (14.9)	159 (14.9)
Ethnicity				
White	329 (93.5)	314 (89.2)	326 (93.4)	969 (92.0)
Other ethnic groups	23 (6.5)	38 (10.8)	23 (6.6)	84 (8.0)
Employment				
Working	222 (62.4)	216 (60.7)	221 (62.3)	659 (61.8)
Not working	134 (37.6)	140 (39.3)	134 (37.7)	408 (38.2)
Education				
No qualifications	9 (2.5)	7 (2.0)	15 (4.2)	31 (2.9)
GCSE equivalent	84 (23.6)	81 (22.8)	62 (17.5)	227 (21.3)
AS/A level equivalent	96 (27.0)	76 (21.3)	81 (22.8)	253 (23.7)
Higher education	167 (46.9)	192 (53.9)	197 (55.5)	556 (52.1)
Longstanding illness/disability				
Myself	89 (25.3)	70 (19.8)	85 (24.1)	244 (23.1)
Someone in the household	37 (10.5)	40 (11.3)	39 (11.1)	116 (11.0)
No	226 (64.2)	244 (68.9)	228 (64.8)	698 (66.0)

Data are *n* (%)

GCSE General Certificate of Secondary Education (UK), *PIL* patient information leaflet

is compromised [13], we did not find evidence for this. Absolute risk perceptions were recorded as an indicator of informed consent, and the results were mixed. Positive framing using natural frequencies produced more correct responses than the same PIL using percentages, replicating previous research showing natural frequencies produce more correct risk estimates than percentages in current PIL formats [31]; however, the positively framed PIL using natural frequencies performed on par with the current PIL. In addition, there was no difference between the PILs in terms of participants' satisfaction of information in the PIL or ratings of credibility. As such, given positive framing using natural frequencies significantly reduced side-effect expectations, performed equally compared with the current PIL in terms of participants' ability to give informed consent and was not viewed negatively by participants, this would seem the logical choice to use in PILs. In addition, future work focusing on the positive framing aspect of PILs should use natural frequencies.

Interestingly, even with the statistical risk accompanying the verbal risk descriptor, 14–84.6% of participants still provided incorrect absolute risks depending on which side-effect was asked about. This supports previous studies [20] and shows that even with the statistical risk information, many patients who read these leaflets do not understand it. Particularly noteworthy was that the current PIL performed poorly on communicating the risk for the side-effect diarrhoea (Very common, more than 1 in 10), with 84.6% of participants providing incorrect absolute risks (87.9% of which were underestimations). This was not reflected in participants' side-effect expectations, however. Perhaps the term 'more than' is too vague and therefore participants base their estimations on the more concrete '1 in 10' statistic.

All leaflets also performed poorly on informing people about their risk of getting any side-effects, with under a third of participants getting the absolute risk of 'any side-effect' correct, with this also being the item causing the greatest

Table 3 Distribution of side-effect likelihood responses across the three PILs

Side-effect likelihood distributions	Current PIL ($n=356$)	Positive frame natural frequencies ($n=356$)	Positive frame percentages ($n=355$)
Diarrhoea			
Very unlikely	26 (7.3)	76 (21.3)	71 (20.0)
Unlikely	106 (29.8)	188 (52.8)	202 (56.9)
About as likely as not	92 (25.8)	58 (16.3)	55 (15.5)
Likely	82 (23.0)	23 (6.5)	17 (4.8)
Very likely	41 (11.5)	4 (1.1)	3 (0.8)
Don't know	9 (2.5)	7 (2.0)	7 (2.0)
Nausea			
Very unlikely	33 (9.3)	78 (21.9)	81 (22.8)
Unlikely	129 (36.2)	189 (53.1)	206 (58.0)
About as likely as not	95 (26.7)	56 (15.7)	38 (10.7)
Likely	76 (21.3)	27 (7.6)	21 (5.9)
Very likely	19 (5.3)	1 (0.3)	3 (0.8)
Don't know	4 (1.1)	5 (1.4)	6 (1.7)
Dizziness			
Very unlikely	74 (20.8)	140 (39.3)	136 (38.3)
Unlikely	160 (44.9)	156 (43.8)	158 (44.5)
About as likely as not	85 (23.9)	40 (11.2)	40 (11.3)
Likely	28 (7.9)	11 (3.1)	12 (3.4)
Very likely	3 (0.8)	3 (0.8)	0 (0.0)
Don't know	6 (1.7)	6 (1.7)	9 (2.5)
Anaemia			
Very unlikely	162 (45.5)	220 (61.8)	223 (62.8)
Unlikely	121 (34.0)	88 (24.7)	93 (26.2)
About as likely as not	46 (12.9)	25 (7.0)	22 (6.2)
Likely	12 (3.4)	4 (1.1)	6 (1.7)
Very likely	1 (0.3)	3 (0.8)	0 (0.0)
Don't know	14 (3.9)	16 (4.5)	11 (3.1)
Seizures			
Very unlikely	251 (70.5)	277 (77.8)	285 (80.3)
Unlikely	81 (22.8)	56 (15.7)	51 (14.4)
About as likely as not	13 (3.7)	9 (2.5)	10 (2.8)
Likely	4 (1.1)	3 (0.8)	3 (0.8)
Very likely	0 (0.0)	4 (1.1)	0 (0.0)
Don't know	7 (2.0)	7 (2.0)	6 (1.7)
Any side-effect			
Very unlikely	38 (10.7)	129 (36.2)	147 (41.4)
Unlikely	118 (33.1)	148 (41.6)	144 (40.6)
About as likely as not	98 (27.5)	38 (10.7)	36 (10.1)
Likely	73 (20.5)	22 (6.2)	18 (5.1)
Very likely	25 (7.0)	8 (2.2)	7 (2.0)
Don't know	4 (1.1)	11 (3.1)	3 (0.8)

Data are *n* (%)

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variation in 'don't know' responses between the three conditions. This information is not explicitly stated in PILs and our results demonstrate that it cannot be inferred from the information that is available.

4.1 Implications for Future Research and Practice

The results suggest that guidelines for side-effect communication in patient information leaflets should consider

Table 4 Difference in median side-effect likelihood rankings between the three PILs

Side-effect likelihood	Current PIL ($n=356$)	Positive frame natural frequencies ($n=356$)	Positive frame percentages ($n=355$)	Kruskal–Wallis (χ^2)
Diarrhoea				
Median (IQR)	3 (2–4)	2 (2–2)	2 (2–2)	164.815
Mean rank	681.60	447.65	438.92	$p<0.001$
Nausea				
Median (IQR)	3 (2–4)	2 (2–2)	2 (2–2)	119.180
Mean rank	659.57	472.95	446.14	$p<0.001$
Dizziness				
Median (IQR)	2 (2–3)	2 (1–2)	2 (1–2)	57.098
Mean rank	616.09	476.56	477.32	$p<0.001$
Anaemia				
Median (IQR)	2 (1–2)	1 (1–2)	1 (1–2)	31.627
Mean rank	577.98	482.95	479.59	$p<0.001$
Seizure				
Median (IQR)	1 (1–2)	1 (1–1)	1 (1–1)	9.832
Mean rank	553.14	515.80	503.06	$p=0.007$
Any				
Median (IQR)	3 (2–4)	2 (1–2)	2 (1–2)	169.356
Mean rank	687.56	455.67	430.39	$p<0.001$

IQR interquartile range, *PIL* patient information leaflet

Table 5 Difference in absolute risk perceptions between the three PILs

Side-effect (correct response)	Current PIL ($n=356$)	Positive frame natural frequencies ($n=356$)	Positive frame percentages ($n=355$)	Chi-square (χ^2)
Diarrhoea (1001–2000)				
Correct (%)	55 (15.4)	224 (62.9)	233 (65.6)	227.107
Incorrect (%)	301 (84.6)	132 (37.1)	122 (34.4)	$p<0.001$
Nausea (101–1000)				
Correct (%)	275 (77.2)	246 (69.1)	248 (69.9)	7.161
Incorrect (%)	81 (22.8)	110 (30.9)	107 (30.1)	$p=0.028$
Dizziness (11–100)				
Correct (%)	281 (78.9)	263 (73.9)	256 (72.1)	4.751
Incorrect (%)	75 (21.1)	93 (26.1)	99 (27.9)	$p=0.093$
Anaemia (2–10)				
Correct (%)	285 (80.1)	274 (77.0)	192 (54.1)	68.623
Incorrect (%)	71 (19.9)	82 (23.0)	163 (45.9)	$p<0.001$
Seizure (0–1)				
Correct (%)	284 (79.8)	306 (86.0)	192 (54.1)	103.708
Incorrect (%)	72 (20.2)	50 (14.0)	163 (45.9)	$p<0.001$
Any (1001 +)				
Correct (%)	77 (21.6)	83 (23.3)	113 (31.8)	11.164
Incorrect (%)	279 (78.4)	273 (76.7)	242 (68.2)	$p=0.004$

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using positively framed side-effect information. This will help to reduce side-effect expectations and therefore subsequent side-effect experience [9], which has implications for adherence [4]. Firstly, however, future research needs to test the impact of positively framing side-effect information in a clinical setting with patients taking active medication. Secondly, as there was not much difference between the two forms of positive framing, future research should also test

Table 6 Difference in satisfaction and credibility ratings between the three PILs

PIL evaluations	Current PIL ($n=356$)	Positive frame natural frequencies ($n=356$)	Positive frame percentages ($n=355$)	Kruskal–Wallis (χ^2)
Satisfaction				
Clear				
Median (IQR)	4 (4–5)	4 (4–5)	4 (4–5)	4.936
Mean rank	559.15	524.07	517.31	$p=0.085$
Easy to understand				
Median (IQR)	4 (4–5)	4 (4–5)	4 (4–5)	3.603
Mean rank	554.77	528.31	517.44	$p=0.165$
Words I did not understand				
Median (IQR)	2 (2–3)	2 (2–3)	2 (2–3)	3.934
Mean rank	553.45	532.90	511.09	$p=0.140$
Similar to other leaflets				
Median (IQR)	5 (4–5)	4 (4–5)	4 (4–5)	3.074
Mean rank	552.83	528.31	517.86	$p=0.215$
Informed choice				
Median (IQR)	4 (4–5)	4 (4–5)	4 (4–5)	0.647
Mean rank	532.59	524.19	540.72	$p=0.724$
Understood risks and benefits				
Median (IQR)	4 (4–5)	4 (4–5)	4 (4–5)	0.836
Mean rank	542.42	534.16	523.87	$p=0.659$
Overall satisfaction				
Median (IQR)	4 (4–5)	4 (4–5)	4 (4–5)	0.574
Mean rank	542.12	527.75	530.61	$p=0.750$
Credibility				
Trusted				
Median (IQR)	4 (3–5)	4 (4–5)	4 (4–5)	4.957
Mean rank	506.28	549.28	546.48	$p=0.084$
Accurate				
Median (IQR)	4 (4–5)	4 (4–5)	4 (4–5)	4.565
Mean rank	507.46	544.73	549.85	$p=0.102$
Fair				
Median (IQR)	4 (4–5)	4 (4–5)	4 (4–5)	0.651
Mean rank	524.39	536.27	541.36	$p=0.722$
Tells the whole story				
Median (IQR)	4 (3–5)	4 (3–5)	4 (3–5)	1.638
Mean rank	519.77	547.87	534.37	$p=0.441$
Unbiased				
Median (IQR)	4 (3–5)	4 (3–5)	4 (3–5)	2.140
Mean rank	517.14	549.42	535.44	$p=0.343$

IQR interquartile range, *PIL* patient information leaflet

the benefit of supplementing the information with visuals, such as icon arrays. These have been shown to be useful when communicating evidence about treatment options to patients [32], and may improve the impact of positive framing further. Thirdly, it was striking that the majority of participants underestimated the absolute risk of getting 'any' side-effect in all three conditions. It may be that this, rather than details about individual side-effects, is the most important information need for patients. Future research should explore their perceptions around this further.

4.2 Strength and Limitations

This is a large study, demographically representative of 16- to 75-year-olds in England. Due to concerns that participants

over the age of 75 years who take part in online surveys are not representative of the general population, they were not included in the study. However, compared with previous similar studies [18, 19], our sample did include participants aged 65–75 years, who have some of the heavier medication consumption levels [33]. While the validity of data from online surveys can be questioned due to concerns that participants do not read the questions properly or that they may be distracted with other tasks [34], this may not be an issue [35], and was offset by our exclusion of participants for reading the leaflet too quickly and for getting any one of the attention check questions wrong. Selection bias is more problematic, however, as it is uncertain if market research panels are psychologically representative of the general population's risk perceptions towards medication side-effects.

There is also a challenge finding wording that works for positively framing side-effect risk but yet is still understood by participants; as such, we made two changes to the wording used when describing side-effect risk in order to make it more streamlined and easier to interpret for readers between the current and positively framed PILs. Firstly, we did not include the term 'may affect…' because of concerns that this would make the positively framed leaflets more cumbersome to read and interpret, for example "may not affect 9 in 10 people" is not that straightforward. Secondly, we changed the verbal descriptors for the positively framed leaflets to better match the statistic being presented. This was because keeping the verbal descriptor 'Common' alongside '9 in 10 people are not affected' was seen as a contradiction as people are used to interpreting the verbal descriptor as the risk of getting the side-effect. In addition, other options such as flipping the descriptors around and explaining them as the risk of not getting a side-effect, for example, that it is 'Very rare' not to experience a (very common) side-effect such as diarrhoea also becomes difficult to interpret because of the double negative. As such we chose the wording to best reflect how it could work in clinical practice, but we acknowledge by not constraining the verbal descriptors across the control and positive frame condition we cannot disentangle if results seen were due to changes to the verbal descriptors, attribute framing, or both combined. As small changes to the wording can affect understanding, what is clear is that future research also needs to understand the best way of verbally describing positively framed side-effect risk, as simply flipping the current format is not so straightforward.

It is possible the response option we used to measure absolute risk perceptions could have affected the results. By asking participants for a number out of 10,000, this is more liable to overestimation compared with choosing an answer from a pre-determined set of responses [36]. However, this method does have benefits in this context as it is easier for participants to express small probabilities. In addition, by choosing a response option out of 10,000, participants in all three conditions had to do some conversion from the statistics they were presented with, for example 1 in 10, 9 in 10 or 90%, but this may have not been as cognitively demanding for those presented with natural frequencies. Future research could perhaps measure absolute risk perceptions with half the sample answering in natural frequencies and half answering in percentages to control for this. Although as we know from other studies that percentages are harder to understand than natural frequencies, using this as a response option might not be the best reflection of people's absolute risk perceptions [31, 32].

In addition, the questions revolved around a hypothetical scenario and as such may not be representative of patients who have just been prescribed a new medication. Future research should replicate this study in a clinical sample where participants are given side-effect information about an 'actual' prescribed medication. Not only this, our sample were also highly educated with 75.8% of the total sample having A level qualifications or higher. As such, replication is also needed with those with lower educational status as their interpretation of the side-effect risk presented in the PILs may be different.

5 Conclusion

Positively framed PILs using natural frequencies significantly reduced side-effect expectations without altering informed consent or satisfaction/credibility ratings of the PIL. Replication is needed with patients prescribed new medication and those with lower educational status.

Acknowledgements We would like to thank the study participants for their time in completing this survey, and Penny and team from Ipsos MORI for carrying out the data collection. Ipsos MORI was responsible for the fieldwork and data collection only and not responsible for the questionnaire design, analysis, reporting or interpretation of the survey results.

Author contributions RW developed the research question, design, methodology and carried out the data analysis and write up. IPSOS Mori conducted the field work and data collection. GJR provided input into the design, methodology and data analysis and reviewed the draft manuscript.

Funding This research was funded by the BA/Leverhulme Small research grants scheme awarded to Dr Rebecca Webster (SRG19\190568), derived from the Academy's partnership with the Department for Business, Energy and Industrial Strategy. Dr G. James Rubin is affiliated to the National Institute for Health Research Health Protection Research Unit (NIHR HPRU) in Emergency Preparedness and Response at King's College London in partnership with Public Health England (PHE), in collaboration with the University of East Anglia and Newcastle University. The views expressed are those of the authors and not necessarily those of the NHS, the NIHR, the Department of Health and Social Care or Public Health England.

Compliance with ethical standards

Conflicts of interest None to declare.

Ethical approval This study was approved by the Research Ethics Committee at King's College London (reference MRA-19/20-14325). All procedures performed in studies involving human participants were in accordance with the ethical standards of King's College London and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. However, we did not publish the protocol on a publicly accessible database as it is not industry standard for market research surveys to be registered in advance.

Informed consent Informed consent was obtained from all individual participants included in the study.

Availability of data and material The datasets generated during the current study are available in the Open Science Framework repository, https://osf.io/mjk9b/

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