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Synopsis

Developing evidence-based guidelines for describing potential benefits and harms within patient information leaflets/sheets (PILs) that inform and do not cause harm (PrinciPILs)

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Abstract

Background: Variation in the way information about potential trial intervention benefits and harms is conveyed within patient information leaflets can cause avoidable information-induced ('nocebo') harm, research waste, and may be unethical.

Objectives:

1. To develop stakeholder-informed principles to guide how to describe information about potential trial intervention benefits and harms within patient information leaflets.
2. To test whether using these principles are feasible for testing in trials that measure whether they improve recruitment and adverse event rates.
3. To develop and disseminate guidance on how to implement the principles.

Methods: We used a mixed methodology consisting of three work packages. Work package 1 involved a modified Delphi survey and consensus meeting to develop the principles for harmonising the way information regarding potential benefits and harms are shared. Work package 2 involved testing whether the principles could be used to transform existing patient information leaflets by recruiting host trials to compare standard patient information leaflets with patient information leaflets developed using the principles 'principled patient information leaflets'. We also set up an infrastructure to test whether they could reduce variation, impact trial recruitment and reduce reported adverse events. Work package 3 involved developing and disseminating guidance for using the principles.

Results: For work package 1, 250 participants completed the Delphi survey and 7 principles were agreed upon: (1) all potential intervention harms should be listed, (2) potential harms should be separated into 'serious' and 'less serious', (3) if not all potential harms are known, this needs to be explicitly stated, (4) all potential benefits should be listed, (5) potential benefits and harms associated with trial participation need to be compared with those associated with non-participation, (6) suitable visual representations should be added where appropriate, and (7) information about potential benefits and harms should not be separated by more than one page. For work package 2, we developed principled patient information leaflets for five host trials and interviewed two members of each host trial team. Two host trials agreed to compare the patient information leaflets with principled patient information leaflets using Studies Within a Trial, and we published a protocol for a meta-analysis that will synthesise the results.

This synopsis should be referenced as follows:
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For work package 3, 25 participants attended a hybrid workshop and recommended that researchers and Research Ethics Committee members should use the principles to design and evaluate patient information leaflets. We produced a guidance booklet and website, which are currently being used by some Health Research Authority Research Ethics Committees.
Conclusions: A strong consensus was reached regarding seven principles that can harmonise the way information about the potential benefits and harms of trial interventions is shared. The principles are likely to reduce research waste and avoidable information-induced harm, and may enhance clinical trial ethics.
Limitations: Due to COVID-19, the National Institute for Health and Care Research review of ongoing trials that resulted in funding termination for several trials, and highly pressured trial staff with limited capacity to add Studies Within a Trial to their trials, we had to modify our second objective. Whereas we initially intended to actually conduct the Studies Within a Trial, we replaced this with: a protocol for a meta-analysis of Studies Within a Trial, additional research on the need to reduce variation, additional dissemination work, and a paper on the ethical requirement to mention potential benefits and harms of trial interventions in patient information leaflets.
Future work: Future work could apply these results to explore how to harmonise the way potential benefits and harms are shared during verbal conversations between researchers and patients during the informed consent process.
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A plain language summary of this synopsis is available on the NIHR Journals Library Website https://doi.org/10.3310/GJJH2402.

Introduction

This report details the work undertaken to establish guidance on sharing information about potential benefits and harms within patient information leaflets (PILs) in a way that is ethically justifiable, consistent and does not induce avoidable harm ('nocebo effects'). It arose from a Medical Research Council (MRC)-funded project, 'Developing and Testing Patient Information Leaflets (PILs) that Inform and do not Cause Harm (PrinciPILs)'.[1]

Details of methods and findings are reported fully in a number of publications (see *Award publications* and *Additional outputs*) and are summarised in the *Methods* section below.

Research and policy context, including rationale, for this study

Three related background problems motivated our project: unexplained variation in how potential benefits and harms of trial treatments are shared within PILs; (relatedly) the variation may cause research waste; and likely harm caused by sharing information about potential benefits and harms in an unbalanced way.

Variation in the extent to which potential benefits and harms of trial treatments are described within patient information leaflets

There is unexplained variation in the extent to which information about potential benefits are shared within PILs. We demonstrated this in an analysis of 33 PILs identified from the International Standard Randomised Controlled Trials Number Clinical Trials Registry. We found that all studies presented information about adverse events (AEs), whereas only a third presented information about intervention benefits. These findings were published in a *Trials* article,[2] highlighting that potential harms appear to be overemphasised, with potential benefits mentioned much less frequently. The finding that the extent to which all potential benefits and harms are described within PILs is variable was confirmed in a study with a larger sample of 214 PILs.[3]

Variation is not an inherent problem, if there are justifiable reasons for sharing information about potential benefits and harms in different ways. However, we could not identify such reasons. Relatedly, there is sometimes a discrepancy in what information patients want and the information Research Ethics Committee (REC) members believe is required.[4] Perhas exacerbating the problem, there does not seem to be sufficient guidance regarding the best way to share information about potential benefits and potential harms. While official guidance from the UK,[5] the USA,[6] the European Union[7] and the international organisations[8] state that information about potential benefits and harms should be shared, they do not specify how.

Policy and ethical problems related to unexplained variation in the extent to which potential benefits and harms are mentioned within patient information leaflets

Lack of guidance regarding how to present information about potential benefits with information about potential harms can lead to research waste in several ways. First, if a PIL overemphasises harms and fails to mention benefits, it can scare some people away from taking part in a trial that might help them.[9] Failure to recruit people for clinical trials is a main cause of trials failing to produce reliable results,[10] which contributes to a waste of public and private funds.[11] Second, researchers and RECs do not have clear guidance to

follow when determining how to present information about potential benefits and harms. This lack of clear guidance can cause waste by duplicating efforts to determine the best way to share information about potential benefits and harms. Third, without clear guidance, REC decisions are more likely to lack consistency, which undermines their justifiability.

There is also a more fundamental ethical dimension to the problems with the variation in the way potential benefits and harms are described within PILs. Clinicians, including those involved in clinical trials, are ethically bound to not cause avoidable harm (non-maleficence) and to help patients whenever they can (beneficence). If the variation in the extent to which potential intervention harms are emphasised compared with potential benefits causes information-induced harm, and such harm can be avoided, then the variation threatens to violate the ethical principle of non-maleficence.[4]

Failure to balance description of potential harms with description of potential benefits (when they exist) can cause harm

Failure to balance information about potential harms with information about potential benefits can cause information-induced harm ('nocebo effects') . We showed this in a systematic review,[12] which included data from over 250,000 patients who took placebos within clinical trials. Half of these participants reported at least 1 AE, with 1 in 20 reporting such serious AEs that they dropped out of the trial. The AEs reported included abdominal pain, burning, chest pain, chills, diarrhoea, dry mouth, dyspepsia, fatigue, insomnia, somnolence, taste disturbance, nausea, vomiting, headache and dizziness. Most were not caused by the placebo treatment or information;[13–15] rather, they were misattributions. For example, many people experience mild pain but, unless they are in a clinical trial, do not report it. However, when they are part of a clinical trial, they report these symptoms that get misattributed to the trial treatment (in these cases, the placebo treatment). To control for misattribution, we identified trials that had treatment, placebo and no treatment groups. We found that there were more AEs reported in the placebo groups than the untreated groups (6.5% vs. 4.3%), suggesting that at least some of the AEs in the placebo group are not misattributions and are likely to have arisen due to the overemphasis of potential harms within PILs. Developing unrealistically negative expectations regarding harms of interventions is known as 'therapeutic misconception'.[16] Paradoxically, the opposite can also occur. If people are not informed about potential benefits, they can develop unrealistically positive expectations about benefits and agree to take medications that are unlikely to benefit them but could cause harm; this is known as 'therapeutic optimism'.

Summary of rationale for research

In summary, the way information about potential trial intervention benefits is provided within PILs varies widely.[2,3] This variation is difficult to justify and is likely to cause avoidable 'nocebo' harms and research waste and could compromise the ethical position of clinicians involved in clinical trials. Relatedly, we lack a robust, evidence-based and stakeholder-informed framework to inform researchers and REC members about the best ways to describe potential benefits and potential harms within PILs. We, therefore, designed this research, 'Developing evidence-based guidelines for describing potential benefits and harms within patient information leaflets/sheets (PILs) that inform and do not cause harm' to develop and disseminate principles to inform future descriptions of potential benefits and harms within PILs.

Aims and research questions

Aims

To develop and disseminate stakeholder-informed principles of good practice to guide how to share information about potential trial intervention benefits and harms within PILs that is balanced, is ethical and does not cause avoidable harm.

Research objectives

We had six specific objectives to achieve our aims.

1. To gather stakeholder views about how information about potential trial intervention benefits and harms should be shared within PILs.
2. To produce principles to guide how to share information about potential benefits and harms of trial interventions within PILs.
3. To transform existing PILs into PrinciPILs by applying the principles.
4. To create the infrastructure for evaluating the effect of PrinciPILs on recruitment rates and AEs within clinical trials.
5. To explore the ethical issues related to the variation in the way potential benefits and harms of trial treatments are mentioned within PILs.
6. To produce user-friendly guidance for RECs.

Protocol

Protocols for the different parts of this work were published separately. A description of the proposed study was published on the UK Research and Innovation website.[1] A protocol for the Delphi survey, which generated the seven principles, was published on the Open Science Framework.[17] A protocol for the meta-analysis of Studies Within a Trial (SWATs) was published on F1000Research.[18]

Methods

Overview

The objectives were addressed by three work packages (WPs). The objectives and methods of each WP are outlined below, with a summary of what was done and any aspects that were not fully realised. We also discuss alterations to our original plans in the Discussion and interpretation. *Figure 1* illustrates how the different WPs link together.

Work package 1: developing the principles using a modified Delphi survey and consensus meeting

The aim of this WP was to discover principles to guide whether and how potential benefits of trial treatments should be mentioned alongside potential harms. A protocol for this part of the research was published in the *Open Science Framework*,[17] and the results of this process were published in *Trials*.[19] *Figure 2* contains an overview of the process.

Development of the list of statements for the Delphi survey

We produced an initial long list of potential principles from:

1. Principles and examples from our review of UK PILs;[2]
2. Extracted principles and examples from a random sample of Drug Facts Boxes;[20] and
3. Statements from official guidance regarding how to present trial benefits and harms.

The official guidance came from within the UK,[21] the European Union,[22] the World Health Organization[23] and the United States Food and Drug Administration.[24] The items were deduplicated.

Participant identification and sample size

Representatives from relevant stakeholder groups: patient representatives, trial participants, clinicians, ethicists, medicolegal experts, psychologists and trial managers. We aimed for at least 10 participants per stakeholder group.

Survey

A survey was developed online using Qualtrics [Qualtrics software, version May–November 2021 of Qualtrics. Copyright © 2021 Qualtrics. URL: www.qualtrics.com/uk/ (accessed 15 March 2024)]. The survey included four vignettes to help participants understand the variation in current practice regarding how to present information about potential benefits. Participants were asked to rate their agreement or disagreement with the statements using a scale from 1 to 9, where 1 corresponds to 'strongly agree' and 9 corresponds to 'strongly disagree'.

Definition of consensus

Following recommended cut-offs for Delphi studies,[25] we defined consensus as follows:

- *Consensus in*: agreement of ≥ 70% of respondents that a principle should be followed when describing information about potential benefits and harms.
- *Consensus out*: agreement of ≥ 70% of stakeholders that a principle should not be followed when describing information about potential benefits and harms.
- *No consensus*: anything else.

Consensus meeting

For the final step of this modified Delphi process, we convened an online meeting with the co-applicants and two

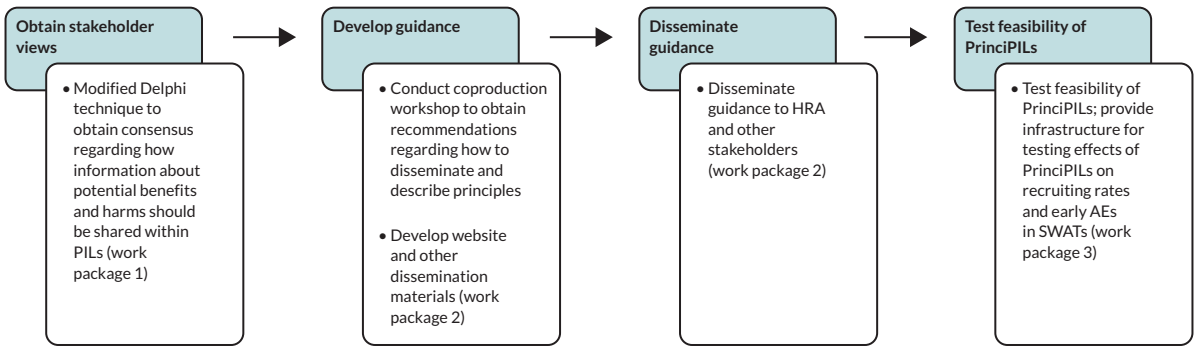


FIGURE 1 Diagram of research pathway showing how each element of the research linksthe other.

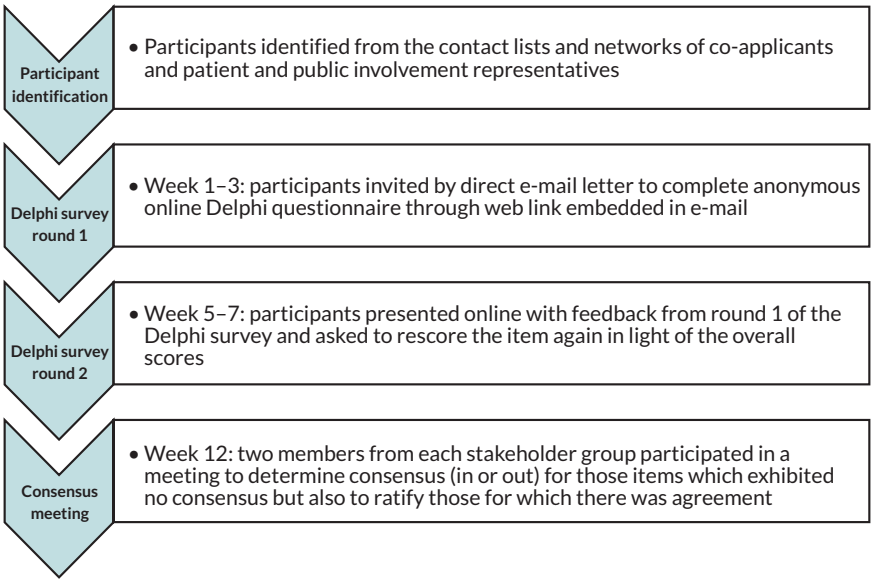


FIGURE 2 Developing principles for sharing information about potential benefits and harms within PILs: overview of process.

members from each stakeholder group. The meeting aimed to determine consensus (in or out) for those items which exhibited no consensus and to confirm those items for which there was agreement. A secondary aim of the meeting was to remove redundant questions and discuss best wording for principles.

Work package 2: developing and making recommendations for disseminating guidance

Developing guidance

To determine what resources would be useful and useable for stakeholders, we held a coproduction workshop. A full report on this was published in National Institute for Health and Care Research (NIHR) Open Research.[26] The aim of the workshop was to coproduce recommendations for developing:

1. User-friendly guidance for users of the principles.
2. Resources that support the implementation of the principles.

To attempt to avoid being distracted by revisiting the principles, we sent an information package to participants one week before the workshop in which the aims were stated, and the evidence base for the principles was described.

Participants from the workshop were purposefully sampled from among those who participated in the Delphi survey and agreed to be contacted.[19] Iterative rounds of feedback and discussion were conducted to explore questions related to the research aims, with opportunities to raise conflicting opinions provided. Extensive low inference style ethnographic notes were taken and expanded following the meeting. Key points were reflected and summarised, and areas of widespread agreement and of disagreement were noted.

Work package 3: developing and testing the feasibility of principled patient information leaflets

The aim of this WP was to take existing PILs and use the seven principles developed in work package 1 to transform them into PrinciPILs, then test whether PrinciPILs impacted on early recruitment rates and AEs.

Transforming patient information leaflets into principled patient information leaflets

We used the seven principles developed to transform existing PILs into PrinciPILs for five host trials[27–31] (*Table 1*), to check whether it was feasible to generate PrinciPILs with investigators who were unfamiliar with them. We published the results of this phase on the Open Science Framework.[32]

The PrinciPILs were generated from these PILs in five overlapping phases.

1. The research team made initial adjustments to the host trial PILs so that the seven principles were adhered to.

TABLE 1 List of host trials

ALABAMA (Trial 2)[28]	A multicentre, two parallel-arm, open-label, individually randomised pragmatic trial aimed at finding out if people with a penicillin-allergy label in their general practitioner health records really do have an allergy by specialist Penicillin-Allergy Assessment Pathway testing
ATLANTIS (Trial 1)[27]	A two-arm, randomised, double-blind, placebo-controlled trial. Patients with a diagnosis of schizophrenia or schizoaffective disorder on an antipsychotic (non-clozapine) for at least 6 weeks, continuing to have positive psychotic symptoms, will be randomised 1 : 1 to either placebo + continuing antipsychotic treatment arm or valproate + continuing antipsychotic treatment arm
PICCOS (Trial 5)[31]	A randomised trial to compare usual chemotherapy (various) with a new way of giving chemotherapy called Pressurised IntraPeritoneal Aerosolised Chemotherapy or PIPAC (delivering chemotherapy as a spray directly into the abdominal cavity during keyhole surgery) in patients with colorectal, ovarian or stomach cancer with peritoneal metastases
Placement (Trial 4)[30]	A randomised trial testing a method for reducing pain [perineural local anaesthetic catheter (PNC)] after major lower-limb amputation. This is a trial of an investigational medicinal product; the intervention is the PNC
VELRAD (Trial 3)[29]	A feasibility randomised controlled trial of performing a videoendoscopic radical inguinal lymphadenectomy vs. open radical inguinal lymphadenectomy in men diagnosed with penile or urethral cancer requiring inguinal lymphadenectomy

2. Interviews with members of the stakeholder group who developed the principles were conducted to check whether they had been implemented correctly. Members of the stakeholder group included public and patient representatives, REC members, industry, applied researchers, and research nurses. Adjustments were made to the PrinciPILs following this step where required.
3. The provisional PrinciPIL was then sent to the host trial leads for feedback and further modification as required.
4. The provisional PrinciPIL was then sent to plain English experts to ensure the PrinciPIL was understandable to a wider audience.
5. Use of figures and graphic design elements were used where feasible.

We classified the degree of the change required as none (no or small changes), minor (minor editing), moderate (rewriting) and major (extensive rewriting or additions).

Deviation from protocol

We had two deviations from our protocol. First, we originally sought to compare PrinciPILs with standard PILs in three SWATs. However, the pandemic and an NIHR funding review of trials presented a challenge to recruiting enough host trials in time. We therefore set up an infrastructure to analyse the results from two SWATs when data becomes available. We also focused on the benefits to patients, researchers and RECs of reducing unwanted variation in the way potential benefits and harms are described within PILs. This change in original plans resulted in four additional activities:

1. We published a protocol for a meta-analysis of future SWATs that compare PrinciPILs with standard PILs.[18] The protocol for the meta-analysis also includes a pilot data extraction form that will permit rapid publication once the results come in.
2. We uploaded a summary protocol for a SWAT of PrinciPILs versus standard PILs on the SWAT Store.[33]
3. To confirm the need to reduce variation within PILs, we conducted an analysis of recent standard PILs to check the extent to which they adhere to the seven principles. While it is unreasonable to expect that the principles be adhered to in advance of being disseminated, this research explored the extent to which there is variation with respect to the principles within existing PILs. If there were variation, it establishes the need for PrinciPILs independently of whether they affected recruitment rates or early AEs. This analysis has been published in *Trials*.[3]
4. To explore the theoretical need to reduce variation in the extent to which potential benefits and harms are described within PILs, we investigated the potential ethical implications of failure to balance information about potential benefits and harms. This study has been published in *Trials*.[34] The ethical issues related to the provision of information was also reported in a book published by the principal investigator.[35]

The second deviation from our protocol was our change to the patient engagement plans. We initially planned to conduct a face-to-face patient engagement activity.

However, the pandemic prevented this. We therefore designed and produced a short video aimed at a lay audience that explains our research.[36]

Results summary

We report our findings in the following logical order (with the related WP and objective indicated in brackets):

1. An exploration of stakeholder views regarding how information about potential benefits should be described alongside information about potential harms of trial treatments (WP1, objectives 1, 2).
2. An examination of the process by which existing PILs can be transformed into PrinciPILs (WP2, objective 3).
3. Development of an infrastructure for evaluating the effects of PrinciPILs compared with standard PILs on early AEs and recruitment rates (WP2, objective 4).
4. An exploration of ethical issues related to the description of potential benefits alongside potential harms (WP2, objective 5).
5. A description and evaluation of dissemination materials produced (WP3, objective 6).

Stakeholder views regarding how information about potential benefits should be described alongside information about potential harms of trial treatments

After removing duplicates, our long list of potential statements included 27 items. Two-hundred and fifty participants responded to the first survey round, and 201 for the second and final round (*Table 2*), and all regions of the UK and all stakeholder groups were represented.

Following the second round of the Delphi survey, consensus was reached for 19 statements. The subsequent consensus meeting consolidated these findings and agreed on seven principles:

1. All potential intervention harms should be listed.
2. Potential harms should be separated into 'serious' and 'less serious' categories.
3. If not all potential harms are known, this should be explicitly stated.
4. All potential benefits should be listed.
5. The potential benefits and harms associated with participation need to be compared with those associated with non-participation.
6. Suitable visual representations should be added where appropriate.
7. The information about potential benefits and harms should be presented in proximity to one another.

Transforming existing patient information leaflets into principled patient information leaflets

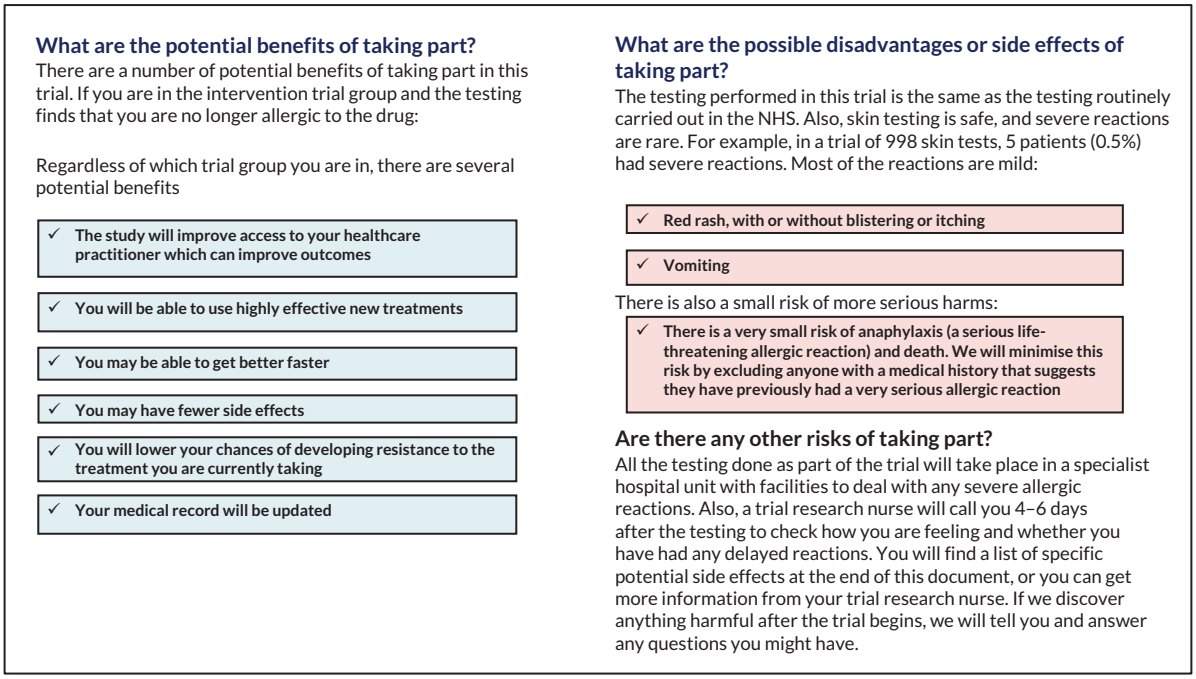
We found that all original PILs required changes to become PrinciPILs (*Table 3*). Adhering to principle 1 (all potential harms should be listed) and principle 3 (stating that all potential harms are not known) required minor or moderate changes. Adhering to the remaining principles required major or moderate changes. Host trial leads were able to make clarificatory suggestions for all PILs. In all cases, they approved of the final version of the PrinciPIL. Reflecting evidence in this area,[37] there was a lack of consensus regarding the best way to use figures or visual representation. We, therefore, made minor yet impactful design modifications (*Figure 3*). Our overall conclusion from this phase was that it was feasible to change existing PILs into PrinciPILs and that researchers can use the principles.

TABLE 2 Delphi survey participant characteristics

Stakeholder group	Participants in round 1 (n = 250)	Participants in round 2 (n = 201)
Public and patient representatives	57	46
REC members and other approvals staff	36	33
Industry (including medicolegal experts)	24	15
Applied researchers, including psychologists and risk communicators	26	18
Research nurses, clinical trial managers and triallists	84	74
Others (including quality assurance managers, quality assurance auditors, clinical auditors, pharmacists, PhD students, sponsor representatives, research midwives and principal scientists)	23	15

TABLE 3 Degree of changes made to PILs

Trial number	Principle 1	2	3	4	5	6	7
1							
2							
3							
4							
5							
Colour code		*No or small change*		*Moderate change*		*Major change*	



What are the potential benefits of taking part?

There are a number of potential benefits of taking part in this trial. If you are in the intervention trial group and the testing finds that you are no longer allergic to the drug:

Regardless of which trial group you are in, there are several potential benefits

- ✓ The study will improve access to your healthcare practitioner which can improve outcomes
- ✓ You will be able to use highly effective new treatments
- ✓ You may be able to get better faster
- ✓ You may have fewer side effects
- ✓ You will lower your chances of developing resistance to the treatment you are currently taking
- ✓ Your medical record will be updated

What are the possible disadvantages or side effects of taking part?

The testing performed in this trial is the same as the testing routinely carried out in the NHS. Also, skin testing is safe, and severe reactions are rare. For example, in a trial of 998 skin tests, 5 patients (0.5%) had severe reactions. Most of the reactions are mild:

- ✓ Red rash, with or without blistering or itching
- ✓ Vomiting

There is also a small risk of more serious harms:

- ✓ There is a very small risk of anaphylaxis (a serious life-threatening allergic reaction) and death. We will minimise this risk by excluding anyone with a medical history that suggests they have previously had a very serious allergic reaction

Are there any other risks of taking part?

All the testing done as part of the trial will take place in a specialist hospital unit with facilities to deal with any severe allergic reactions. Also, a trial research nurse will call you 4–6 days after the testing to check how you are feeling and whether you have had any delayed reactions. You will find a list of specific potential side effects at the end of this document, or you can get more information from your trial research nurse. If we discover anything harmful after the trial begins, we will tell you and answer any questions you might have.

FIGURE 3 Example patient information leaflet describing potential benefits and harms that using improved design. Note: Based on actual example with details removed so host trial PIL is not identifiable.

Development of a pathway to evaluate the effects of principled patient information leaflets compared with standard PILs on early adverse events and recruitment rates

Studies Within a Trial of principled patient information leaflets versus standard patient information leaflets

Two of the host trials for which we developed PrinciPILs are conducting SWATs,[27,31] and we are awaiting the results. The results will be analysed in the context of the meta-analysis protocol we developed and published.[18]

Analysis of variation within standard patient information leaflets with respect to the seven principles

Our analysis of 214 standard PILs to check the extent to which they adhere to the seven principles revealed considerable variation. None of the PILs used more than four principles, and some (4%) used none. Twenty-seven per cent of all PILs presented information about all known potential harms, whereas 45% presented information on all potential benefits. Some PILs did not list any potential harms or potential benefits (8%). The variation in information contained within PILs

held for adult and children PILs and across disease areas.

Exploration of ethical issues related to the description of potential benefits alongside potential harms

We wrote a paper on the relationship between the principles generated by this research, the four principles of medical ethics (beneficence, non-maleficence, autonomy and justice) and the requirement for informed consent.[34] The related ethical issues were also reported in a book published by the principal investigator.[34]

Developing and making recommendations for disseminating guidance

Twenty-five participants, including representatives from the HRA, REC members and trial managers, attended a hybrid workshop and made useful suggestions for developing guidance and resources.

User-friendly guidance for users of the principles

Participants made the following recommendations:

1. **Guidance should be useable by researchers designing PILs and ethics committee members**. Initially, there was uncertainty whether all main user groups of the principles (researchers, patients, REC members) should have separate guidance or whether they could all use the same guidance. The group was clear that the same guidance could and should be used.
2. **The proper use of appendices needs to be clarified.** In our example PrinciPILs, some potential harms and benefits were listed in appendices, which are sometimes used to avoid overly lengthy risks and benefits sections in PILs. The extent to which these are accessed by participants was queried, although it was agreed that their use may sometimes be required to ensure readability.
3. **Examples of visual representation should be provided.** The types of visual representation of risks that would be appropriate were not clear to the attendees. The attendees recommended that if this principle was to be used, that examples of visual representation be provided.
4. **The rationale for including information about potential benefits should be clear**. Two vociferous participants insisted that mentioning potential benefits within PILs was not justified. This was disputed by the remaining participants.
5. **The evidence base underpinning the principles must be highlighted.**

The workshop participants also made a number of suggestions for clarifying all seven principles.[26] The most substantive of these was a suggestion to clarify what constituted a benefit. We addressed this in our paper on the underlying ethical issues related to our project.[34]

Resources that support the implementation of the guidance

Two main suggestions were made regarding resources for implementing the guidance. First, participants noted that appropriate implementation of resources is relative to the target audience. For example, researchers need more detailed instructions, whereas ethics committees may require exemplars. When developing resources, it would be useful to test these with different RECs. It was suggested that this could be achieved with worked examples. Second, participants agreed that a strength of the principles is their brevity. It was even suggested that a single-page explanation of the seven principles could suffice for most audiences.

Dissemination and dissemination materials

Based on the recommendations from the coproduction workshop, we developed several resources:

1. A user-friendly guidance booklet.[38] This short 11-page guidance booklet lists all the principles, instructions for how to include the principles into standard operating procedures, examples, a link to the video and links to the underpinning research.
2. Websites:
   a. Cardiff University website.[39] This permanent website describes the PrinciPIL project, has links to the guidance document as well as examples of PrinciPILs.
   b. Bespoke website.[40] The bespoke website contains much of the information that the guidance document has, with a link to the video.
3. A video[36] aimed at a lay audience was produced that demonstrates the benefits of PrinciPILs.

We also engaged in several dissemination activities. Our most impactful dissemination activity involved engaging with the HRA so that our principles were accepted as standard practice by all UK HRA RECs. We engaged with the HRA from the outset of the project to ensure that the form and content of our results were relevant to them. This activity has been successful, and we have delivered several webinars to REC leads via the HRA. This activity has been bolstered by collaboration with the Oxford REC A, which now uses our principles to adjudicate whether the information about potential benefits and harms

within PILs is adequate. We are delivering a webinar about the principles in December 2023 to the HRA (see *Further funding for future work*).

We have engaged in several other dissemination activities to encourage the adoption of our principles.

- **Peer-reviewed publications**: Ten peer-reviewed publications have resulted from this project (see *Award publications*). We have also published our guidance (see *Additional outputs* below). Our paper describing the process of developing the principles was ranked in the 95th percentile (ranked 8th) of 163 tracked articles of a similar age in *Trials*.[19]
- **Conferences**: We have delivered several seminars to explain the seven principles, including Novonordisk, the European Forum for Good Clinical Practice, the MRC and Trial Forge.
- **Social media:** We disseminated the results of our key publications via social media. Upon completion of the project, we posted a 'Tweetorial' that had 2635 impressions (as of 25 August 2023).[41]
- **Public engagement:** Our video script was developed with our patient representative and a professional film company to ensure it is accessible and understandable to a lay audience.[36]
- **Education and training.** We have been engaged to deliver an educational webinar for HRA REC leads.

Discussion and interpretation

Principal findings and achievements per project outcome

We were able to show that it is possible to reduce unwanted or unexplained variation in the way potential benefits and harms of trial interventions are shared within PILs and produce materials to facilitate rapid dissemination. Reducing the variation has the potential to reduce research waste, reduce 'nocebo' harms and enhance the justification for REC decisions about what should and should not be included about potential benefits and harms within PILs.

By including a large sample of nationally representative respondents (n = 250) from a variety of stakeholders, we were able to gain an understanding of what patients and other stakeholders believe is the right way to balance information about potential benefits alongside information about potential harms within PILs. We were also able to gain clear consensus on seven guiding principles to guide the way information about potential benefits and harms are shared within PILs.

Additionally, we were able to show that it is possible to change current practice by transforming five standard PILs into PrinciPILs using a simple five-step process. This demonstrates that it is feasible to change current practice. We also successfully recruited two host trials who are currently comparing the effect on recruitment and early AEs of PrinciPILs versus standard PILs, and created an infrastructure so that results of these (and other future trials of PrinciPILs) can be easily analysed.

Our coproduction workshop with 25 stakeholders generated useful suggestions for developing and disseminating the guidance. The suggestions included instructions to keep things simple and to ensure that the evidence base for the principles was clear. We were able to develop this guidance through a short document and two websites and disseminate it to key stakeholders, including the HRA. We overcame COVID-19 restrictions and engaged patients via a video.

The consensus we were able to achieve across many stakeholders contrasts with the variation in current practice. Our two analyses of current PILs clearly demonstrated variation in the extent to which potential benefits are mentioned and in the extent to which the principles are reflected within them. Potential benefits are sometimes not mentioned at all, and an exhaustive list of potential harms is often not included.

Despite challenges related to NIHR funding, we were able to implement our SWATs of PrinciPILs versus standard PILs for two host trials, and we have set up an infrastructure to analyse the results in the future.

Our project also facilitated the career advancement of several team members. Two team members (Martina Svobodova, Nina Jacob) won research awards for presenting work related to the project, and two others (Jeremy Howick, Katie Gillies) were promoted to professor during the tenure of the award.

Contribution to existing knowledge

Our project adds to three main bodies of literature: HRA and other ethical guidance on the need to share information about potential benefits and harms, literature on methods for improving recruitment and retention in trials, and literature on the need to involve patient views in methodological research.

Adding to the literature on guidance for obtaining informed consent

Our research contributes to the acknowledged need for more consistency in how research ethics principles are applied when it comes to describing potential benefits and harms,[42] with some calling for standardised guidelines.[43] 'Drug Facts Boxes' are an example of attempts to do this.[20] However, these boxes are specific to the pharmaceutical sector and are not directly relevant to the UK research and regulatory context. In a related study, it was found that pharmacists adjusted the treatments they offered based on how risks were presented to them.[44] A recent systematic review also highlighted that a clear, optimal method for communicating risks to patients in trials has yet to be established.[37] As such, our project makes a significant contribution to the existing body of research by offering clear, consensus-based guidelines for describing the potential benefits and risks of trial interventions to participants.

We have also helped to fill a gap in the literature related to the lack of clear guidance regarding how to present potential benefits and harms. Whereas the requirement to mention both potential benefits and harms is accepted as a requirement in the UK and elsewhere (*Table 4*), the way this should happen is not, and this has caused variation in practice that is difficult to justify. The only exception to this rule is that sometimes the need to contrast serious with less-serious harms is mentioned.[7] Our findings addressed this, and the principles revealed by our research were broadly in line with current HRA guidance, with some important differences. For example, whereas current relevant HRA guidance is limited (which could be a cause of the variability), our guidance is more extensive. Another important difference is that whereas current HRA guidance states that it is not usually possible to specify potential benefits, our stakeholders were clear that *potential* benefits (which are not certain benefits) should be listed. Our results show that, contrary to common intended practice,[21] greater care must be taken to ensure that trial participants are aware of the potential benefits of trial interventions.

Adding to the literature on improving recruitment and retention in clinical trials

A systematic review of methods to improve recruitment[45] and retention in clinical trials found that certain types of reminders could increase recruitment and retention.[46] Our findings suggest that another strategy could involve improving the way information about potential benefits and harms are shared with trial participants.

Adding to the literature on patient involvement in the development of patient information leaflets

A study published in 2014 by Bjorklund *et al.* highlighted the need for additional research with stakeholder input to identify what information participants require to decide whether to participate in a trial.[47] Our research addresses this gap by including patients and other stakeholders to produce principles that can be applied to improve the information provided within the PILs.

Relationship with other literature

Relationships between our findings and other research are listed below.

1. **Reduced variability and research waste for the researchers designing PILs and ethics committees evaluating them.** Our guidance about how to describe potential benefits and harms shared within PILs will reduce variation, confusion and time for those designing and evaluating PILs that previous research has identified.[2,33]

TABLE 4 Policy documents specifying the requirement to inform trial participants about potential benefits

Country	Quote
(International) Declaration of Helsinki[8]	'Each potential subject must be adequately informed of . . . the anticipated benefits and potential risks of the study'
UK: The Medicines for Human Use (Clinical Trials)[5]	'Before the trial is initiated, foreseeable risks and inconveniences have been weighed against the anticipated benefit for the individual trial subject'
European Union: Regulation (EU) No 536/2014 of the European Parliament and of the Council of 16 April 2014 on clinical trials on medicinal products for human use[7]	'Information given to the subject . . . shall: (a) enable the subject or his or her legally designated representative to understand: (i) the nature, objectives, benefits, implications, risks and inconveniences of the clinical trial'
USA: Office for Human Research Protections[6]	'[I]n seeking informed consent the following information shall be provided to each subject . . . A description of any benefits to the subject or to others that may reasonably be expected from the research'

2. **More understandable and balanced PILs for patients**. The Prioritising Recruitment in Randomised Trials project (http://priorityresearch.ie/) named the following question as the second most important for recruitment research: 'What information should triallists communicate to members of the public who are being invited to take part in a randomised trial in order to improve recruitment to the trial?' Our project helps to meet this objective by providing ways to communicate what potential trial participants wish to know in a way that they understand due to their involvement in developing the principles and guidance.
3. **Improved ethical justification for information contained within PILs.**[4,34] Our findings provide ethics committees with a benchmark against which to evaluate the text within PILs that describes potential benefits and harms.
4. **Reduction of research waste** [11]. Providing balanced information about trial harms and benefits is likely to improve trial recruitment and retention, lowering costs within individual trials.

Additionally, by gathering stakeholder views on how to present information about potential benefits and harms of trial treatments, we were able to add to the existing guidance in a way that can reduce variation (and all the related problems) and could also improve recruitment rates and lower AE rates.

Since the completion of the project, the HRA has asked the principal investigator (Jeremy Howick) to deliver a webinar and asked for guidance on how to incorporate the results into their forthcoming general guidance on the informed consent process. Jeremy Howick has also been invited by the American Society of Bioethics to deliver a seminar to explore how the principles apply to the US setting.

Strengths and weaknesses of the study

The main strength of this study is that it provided the first rigorous, stakeholder-informed, and user-friendly principles that can be used to reduce unwanted and potentially unethical variation in the way information about potential benefits and harms are shared within PILs. The main weakness is related to the failure to recruit host trials for SWATs in a timely fashion (see *Challenges, limitations and reflections* below).[48]

Challenges, limitations and reflections

The main limitation to our study was related to the challenges we faced in recruiting enough host trials to conduct SWATs of the effects of PrinciPILs on recruitment rates and AEs. This limitation will be addressed in the future with the two SWATs we successfully recruited. To mitigate the impact of this limitation, we did additional research showing the need to reduce variation in the way potential benefits and harms are described within PILs,[3] explored how using PrinciPILs could enhance trial ethics and conducted additional dissemination activity.[34]

Another challenge was related to our co-production workshop aimed at generating suggestions for developing and disseminating guidance. Despite preparing the participants by sending them the evidence upon which the principles were based, the participants had not read the evidence, and we spent a great deal of time revisiting the evidence in the workshop. Recommendations for conducting successful coproduction workshops has recently been developed.[49] Although these recommendations were not available at the time we conducted the workshop, we may have been able to do more to prevent the side-tracking of the discussion had we engaged with the evidence about successful coproduction workshops.

A third challenge was related to the pandemic, which caused us to modify planned public engagement work. Initially, we planned to do a live event, such as a play in a public space. We had to replace this part of our research with a video designed for a lay audience. We accompanied the video with a Tweetorial about the project and also wrote a blog for a lay audience.[50] An advantage of the video is that it has the potential to reach a greater audience than a one-off face-to-face event.

Throughout the project, and especially during the coproduction workshop, we encountered resistance from a small but vociferous number of people, mostly members of ethics committees. These individuals insisted on making several related claims related to the desirability of mentioning potential benefits of interventions within PILs. Examples of these claimes included: 'potential harms are known whereas potential benefits are not', 'stating that there are potential harms is coercive' and 'claiming there are potential harms is illegal'. None of these claims is true. Very little about benefits and harms is *known* before the results of a trial are analysed. However, at least in Phase III trials, if there were no potential benefits, it is unlikely the trial would be funded. To address these misunderstandings, we wrote a letter that was published in the *BMJ*[51] and conducted an additional ethical analysis.[34] Upon reflection, we could have addressed these misunderstandings with clearer evidence (such as the evidence presented in *Table 4*) earlier in our project.

Conclusion

We were able to obtain clear consensus on seven principles that can be used to guide how to describe potential benefits and harms of trial treatments within PILs. The consensus we generated contrasts sharply with the variation in the way information about potential benefits and harms is currently shared within PILs. Our user-friendly guidance can and has been used to change PILs into PrinciPILs, and HRA RECs are starting to use the principles in their deliberations. Our findings also contribute to the literature on risk communication, trial recruitment and patient involvement in methodological research. Future research may confirm that the principles could reduce avoidable AEs while improving trial retention and recruitment. Our findings can also be used to inform research on improving the way potential benefits and harms are communicated with trial participants verbally.

Patient and public involvement

A patient and public involvement (PPI) representative (Jennifer Bostock) was involved in acquiring the study funding, question development, research design and background research. The same PPI representative is involved in our ongoing dissemination plan to ensure that the dissemination of our results is understandable and useful for the members of the public.

Equality, diversity and inclusion

The members of our advisory board were chosen partly based on their projected characteristics. We had equal numbers of males and females, two members from ethnic minority backgrounds and one member with a disability. For the consensus meeting that followed our Delphi survey, we selected a group comprising 10 individuals balanced for gender and ethnicity. Relatedly, our coproduction workshop was purposefully sampled to maximise diversity; of the 25 participants, 10 were from ethnic minority backgrounds and 15 were female. The research team itself was representative, with male and female members, members from ethnic minority backgrounds, and experience and expertise across the research team. Future studies may consider ethnicity mix in the stakeholder group.

Impact and learning

What difference has been made already, and what long-term impact might arise?

The HRA RECs are already starting to use the principles developed as part of our research, and this can reduce variability and research waste while bolstering the ethical justification for decisions regarding how to share information about potential benefits and harms within trials. This impact can be formally measured in the future, for example, by replicating our study in the future to measure change in variation.[3] Following the results of our SWATs, our background research suggests that PrinciPILs will improve research waste and reduce information-induced harm. The benefits of improving trial recruitment and retention is considerable: over half of clinical trials fail (often because of recruitment and retention problems),[10] at a cost of hundreds of millions of pounds per failed trial. Reducing the chances of failed trials even by a small amount therefore has the potential for significant positive economic impact. Because successful trials can inform practice, implementing the principles developed as part of this study can also have an impact on patient health.

Research recommendations

Our research gave rise to several questions that we recommend are investigated in future research (listed in priority order).

Question 1: How can the seven principles inform future Health Research Authority (and other regulatory body) guidance on sharing information about potential benefits and harms?

This may be achieved through dissemination activities related to the ones that have been conducted by the research team. It may also require implementation research.

Question 2: (meta-analysis) What are the effects of principled patient information leaflets on trial recruitment, retention and rate of adverse events?

The PrinciPILs potentially improve trial recruitment and retention while reducing the rates of subjectively reported AEs. COVID-19-related delays prevented the completion of the planned SWATs comparing PrinciPILs with standard PILs. Two SWATs are currently underway, and we have created an infrastructure to publish the results of these in a meta-analysis.

Question 3: How can the principles be used to guide verbal conversations with prospective trial participants about potential benefits and harms?

Future work should go beyond the written information about benefits and harms of the trial interventions in two ways. First, research is required to apply our seven principles, perhaps in an adapted format, to the verbal conversations that trial participants have about

This synopsis should be referenced as follows:
Howick J, Svobodova M, Treweek S, Gillies K, Edwards A, Bower P, *et al*. Developing evidence-based guidelines for describing potential benefits and harms within patient information leaflets/sheets (PILs) that inform and do not cause harm (PrinciPILs). *Health Technol Assess* 2025;**29**(43). https://doi.org/10.3310/GJJH2402

intervention benefits and harms. Second, research needs to establish how to best share information (written and verbal) about potential benefits and harms of trial *participation* (which includes but goes beyond potential benefits and harms of trial interventions).

Question 4: Are the seven principles applicable to routine practice?

Our results may eventually be adapted for use in clinical practice, where healthcare practitioners can adapt PrinciPILs to guide the way they share information about the harms and benefits of interventions with participants during routine practice.

Question 5: How can the principled patient information leaflets be applied to describe the potential benefits and harms of trial participation beyond the potential benefits and harms of trial interventions?

This could be answered by designing and evaluating a parallel set of principles related to information about trial participation.

Question 6: What are the longer-term outcomes (e.g. at 5 and 10 years) of principled patient information leaflets?

This question can be answered with additional SWATs that involve longer-term outcomes.

Question 7: How do trial participants view principled patient information leaflets compared with standard patient information leaflets?

This question can be answered with qualitative interviews involving actual or potential trial participants.

Question 8: To what extent do the principles apply to other settings with different regulatory and medicolegal frameworks?

This question can be answered by adapting our study for other countries.

Related work not directly funded by the National Institute for Health and Care Research but arising from this study

The additional research validating the need to implement the seven principles was partly funded by the University College Cork, and the future meta-analysis of SWATs of PrinciPILs will be funded by the Stoneygate Centre for Empathic Healthcare.

Further funding for future work (including with new collaborators)

To maximise the impact of our principles, they must become standard practice and formally supported by the HRA. While we have already produced guidelines, additional research could produce resources that are more directly applicable by the MRC. To achieve this, we will be applying to the MRC 'Develop guidance for better research methods' programme.

Additionally, the core research team are planning a future application to the MRC Better Methods, Better Research to adapt the methodology from this project for verbal conversations about potential benefits and harms of trial interventions.

This future research will be bolstered by collaborations developed as part of this project. In addition to collaborations with the co-applicants' institutions (Cardiff University, Manchester University and the University of Aberdeen), collaborations arose with Professor Frances Shiely from the University College Cork,[3] as well as researchers from the University of York.

Additional information

CRediT contribution statement

Jeremy Howick (https://orcid.org/0000-0003-0280-7206): Conceptualisation (equal), Methodology (equal), Project administration (lead), Supervision (lead), Visualisation (equal), Formal analysis (equal), Writing – original draft (lead), Writing – reviewing and editing (lead), Funding acquisition (lead).

Martina Svobodova (https://orcid.org/0000-0001-7949-4039): Conceptualisation (supporting), Methodology (supporting), Project administration (supporting), Visualisation (equal), Formal analysis (equal), Writing – reviewing and editing (supporting).

Shaun Treweek (https://orcid.org/0000-0002-7239-7241): Conceptualisation (supporting), Methodology (supporting), Writing – reviewing and editing (supporting), Funding acquisition (supporting).

Katie Gillies (https://orcid.org/0000-0001-7890-2854): Conceptualisation (supporting), Methodology (supporting), Writing – reviewing and editing (supporting), Funding acquisition (supporting).

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Nina Jacob (https://orcid.org/0000-0002-3240-4179): Conceptualisation (supporting), Methodology (supporting), Visualisation (supporting), Formal analysis (equal), Writing – reviewing and editing (supporting).

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Patient data statement

This work did not use patient data. The infrastructure we have set up for future meta-analysis involves the provision of summary data from host trials, not individual level patient data.

Data-sharing statement

The qualitative data in this study are not suitable for sharing beyond that contained within the cited publications and this manuscript. Further information, and requests for other data should be addressed to the corresponding author.

Ethics statement

This project was approved by the Health Research Authority (IRAS project ID 305945; REC reference 22/EE/0040) on 16 December 2021.

Information governance statement

Cardiff University is committed to handling all personal information in line with the UK Data Protection Act (2018) and the General Data Protection Regulation (EU GDPR) 2016/679. Under the Data Protection legislation, Cardiff University is the Data Controller, and you can find out more about how we handle personal data, including how to exercise your individual rights and the contact details for our Data Protection Officer here www.cardiff.ac.uk/public-information/policies-and-procedures/data-protection.

Disclosure of interests

Full disclosure of interests: Completed ICMJE forms for all authors, including all related interests, are available in the toolkit on the NIHR Journals Library report publication page at https://doi.org/10.3310/GJJH2402.

Primary conflicts of interest: Jennifer Bostock is a member of the following NIHR committees: NIHR HTA CET (2017–present); NIHR HTA CET Funding Committee (2020–present); NIHR HTA General Committee (2020–present); NIHR HTA Commissioning Funding Committee (2020–present); NIHR HTA Post Funding (CET and GB) Programme Oversight Committee (2020–present); NIHR HTA Post-Funding Committee (Commissioning) (2020–present)

Katie Gillies was a member of the NIHR HTA CET Committee member (2020–2024). Completed ICMJE forms for all authors, including all related interests, will be available in the toolkit on the NIHR Journals Library report publication page.

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This publication presents independent research commissioned by the National Institute for Health and Care Research (NIHR). The views and opinions expressed by authors in this publication are those of the authors and do not necessarily reflect those of the NHS, the NIHR, MRC, NIHR Coordinating Centre, the Health Technology Assessment programme or the Department of Health and Social Care.

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Award publications

This synopsis provided an overview of the research award *Developing and Testing Participant Information Leaflets (PILs) that Inform and do not Cause Harm (PrinciPILs)*. Other articles published as part of this thread are:

Svobodova M, Jacob N, Hood K, Gillies K, Hale R, Bostock J, et al. Developing principles for sharing information about potential trial intervention benefits and harms with patients: report of a modified Delphi survey. *Trials* 2022;**23**:863. https://doi.org/10.1186/s13063-022-06780-1

Jacob N, Howick J, Svobodova M, Treweek S, Gillies K, Edwards A, *et al*. Co-production of guidance and resources to implement principled participant information leaflets (PrinciPILs). *NIHR Open Res* 2023;**3**:42. https://doi.org/10.3310/nihropenres.13423.1

Howick J, Doshi P. On the ethical requirement to inform patients about potential treatment benefits. *BMJ* 2023 Jun 5;**381**:1233. https://doi.org/10.1136/bmj.p1233

Cuddihy L, Howick J, Murphy E, Shiely F. When describing harms and benefits to potential trial participants, participant information leaflets are inadequate. *Trials* 2024 May 1;**25**:292. https://doi.org/10.1186/s13063-024-08087-9

For more information about this research, please view the award page (https://gtr.ukri.org/projects?ref=MR%2FV020706%2F1).

Additional outputs

Research outputs

Svobodova M, Hale R, Hood K, Gillies K, Bostock J, Bower P, *et al*. *Developing Core Principles for Sharing Information about Potential Intervention Benefits and Harms in Patient Information Leaflets Using a Modified Delphi Survey*. Open Science Framework 2021.

Howick J, Sovoboda M, Jacob N, Treweek S, Gillies K, Edwards A, *et al*. *PrinciPIL Guidance for Research Ethics Committees and Researchers*. Cardiff: Cardiff University; 2022. URL: www.cardiff.ac.uk/__data/assets/pdf_file/0006/2719167/Cardiff-University-PrinciPIL-Guidance-Booklet.pdf (accessed 12 June 2025).

Howick J, Svobodova M, Treweek S, Jacob N, Gillies K, Bostock J, *et al*. Patient reported outcomes and recruitment rates following the introduction of principled patient information leaflets. *NIHR Open Research* 2023;**3**:29. https://doi.org/10.3310/nihropenres.13420.1

Howick J, Svobodova M, Jacob N, Treweek S, Gillies K, Edwards A, *et al*. Implementing consensus-based principles to transform patient information leaflets into 'principled patient information leaflets' (PrinciPILs). *osfio* 2023. https://doi.org/10.31219/osf.io/2xpn3

Howick J, Svobodova M, Treweek S, Jacob N, Gillies K, Bostock J, *et al*. Patient reported outcomes and recruitment rates following the introduction of principled patient information leaflets (PrinciPILs): protocol for a meta-analysis. *NIHR Open Res* 2023;**3**:29. https://doi.org/10.3310/nihropenres.13420.1

Howick J, Svobodova M, Treweek S, Gillies K, Bower P, Edwards A. *SWAT 161: 'Principled' versus Usual Approach for Sharing Information about Potential Benefits and Harms of Trial Interventions in Patient Information Leaflets*. SWAT Repository. URL: www.qub.ac.uk/sites/TheNorthernIrelandNetworkforTrialsMethodologyResearch/FileStore/Filetoupload,1358621,en.pdf (accessed 12 June 2025).

Howick J, Lantos JD, Svobodova M, Treweek S, Jacob N, Gillies K, *et al*. Variation in the extent to which patient information leaflets describe potential benefits and harms of trial interventions: a commentary. *Trials* 2025;**26**:132. https://doi.org/10.1186/s13063-025-08824-8.

Howick J. *The Power of Placebos: How the Science of Placebos and Nocebos Can Improve Health Care*. Baltimore: Johns Hopkins University Press; 2023.

Other outputs

Howick J. *Unnecessary Harm Caused by Informed Consent*. Blogs: Centre for Trials Research blog; 2021. URL: https://blogs.cardiff.ac.uk/centre-for-trials-research/unnecessary-harm-caused-by-informed-consent/ (accessed 12 June 2025).

Website hosted by Cardiff University. URL: www.cardiff.ac.uk/centre-for-trials-research/research/studies-and-trials/view/principil (accessed 12 June 2025).

Website designed by PrinciPIL team. URL: https://jeremyhowick.wixsite.com/principil (accessed 12 June 2025).

Video explaining the PrinciPIL study to a lay audience. URL: www.youtube.com/watch?v=ZPtczB11jkQ&t=1s (accessed 12 June 2025).

Talks and conference presentations

Developing Participant Information Leaflets (PILs) That Inform and Do Not Cause Harm (PrinciPILs). Health Research Authority (HRA), London, UK, 5 December 2023.

On the ethical requirement to inform trial participants the truth, the whole truth, and nothing but the truth . . . about potential treatment benefits! University of Maryland. Virtual, 17 October 2023.

Reducing Unwanted Variation and Adverse Events by Explaining Potential Benefits and Harms to Patients. United Kingdom Trial Managers Network (UKTMN) Annual Conference, Birmingham, UK, 13 June 2023.

Developing Participant Information Leaflets (PILs) That Inform and Do Not Cause Harm (PrinciPILs). Novo Nordisk. Virtual, 15 January 2023.

Why Ethics Committees Are Unethical for Not Taking Nocebo Effects Seriously. European Forum for Good Clinical Practice, European Forum for Good Clinical Practice (EFGCP) Annual Conference (Virtual), 16 December 2021.

Placebos Are Blockbuster Drugs. 4th International Mental Health Meeting of Romão de Sousa Foundation, Virtual, 6 November 2021.

Placebos Are Blockbuster Drugs. World Federation of Chiropractic 16th Biennial Conference, Virtual, 23 September 2021.

Developing and Testing Participant Information Leaflets (PILs) That Inform and Do Not Cause Harm (PrinciPILs). Medical Research Council, Virtual, 10 September 2021.

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List of abbreviations

AE	adverse event
HRA	Health Research Authority
MRC	Medical Research Council
NIHR	National Institute for Health and Care Research
PIL	patient information leaflet
PPI	patient and public involvement
PrinciPIL	principled patient information leaflet
REC	Research Ethics Committee
SWAT	Study Within A Trial

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