**Developing Core Principles for PrinciPILs using a Modified Delphi Survey**

**Version 1.0, 26th March 2021**

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| **CTR ref:** | **786** |
| **Q-Pulse Document Template Number:**  | **TPL/003/36** |

**SIGNATURE PAGE**

The undersigned confirm that the following protocol has been agreed and accepted and that the Chief Investigator agrees to conduct the study in compliance with the approved protocol and will adhere to the principles outlined in the relevant study regulations and CTR Standard Operation Procedures (SOPs).

I agree to ensure that the confidential information contained in this document will not be used for any other purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of the Sponsor

I also confirm that I will make the findings of the study publically available through publication or other dissemination tools without any unnecessary delay and that an honest accurate and transparent account of the study will be given; and that any discrepancies from the study as planned in this protocol will be explained.

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|  | Signed via electronic signature (attached email dated 26th March 2021) |  |
| **Name: Prof Kerry Hood** | **Signature** | **Date** |
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| **Name: Dr Jeremy Howick** | **Signature** | **Date** |

**General Information** This protocol describes the Developing Core Principles for principled patient information leaflets (PrinciPILs) using a Modified Delphi Survey study and provides information about the procedures for entering participants into the study. The protocol should not be used as a guide, or as an aide-memoire for the treatment of other participants. Every care has been taken in drafting this protocol; however, corrections or amendments may be necessary. These will be circulated to the known Investigators in the study. Problems relating to the study should be referred, in the first instance, to CTR.

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**Study Co-ordination:**

The PrinciPIL study is being coordinated by the Centre for Trials Research (CTR), Cardiff University, a Clinical Research Collaboration (UKCRC) registered trials unit.

For all queries please contact the PrinciPIL team through the main study email address. Any clinical queries will be directed through the Study Manager to the Chief Investigator (CI).

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**Glossary of Abbreviations**

|  |  |
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|  |  |
| **CF** | Consent Form |
| **CI** | Chief Investigator |
| **CPRD** | Clinical Practice Research Datalink |
| **CRF** | Case Report Form |
| **CTR** | Centre for Trials Research |
| **CTU** | Clinical Trials Unit |
| **EDC** | Electronic Data Capture |
| **EMA** | European Medicine Agency |
| **ERES** | Electronic records and electronic signatures |
| **GCP** | Good Clinical Practice |
| **GDPR** | General Data Protection Regulation |
| **HRA** | Health Research Authority |
| **IC** | Informed consent |
| **ICF** | Informed Consent Form |
| **MRC** | Medical Research Council |
| **NHS** | National Health Service |
| **NIHR** | National Institute for Health Research |
| **NIHR NETSCC** | National Institute for Health Research Evaluation, Trial and Studies Coordinating Centre |
| **PI** | Principal Investigator |
| **PIL** | Participant Information Leaflet |
| **PIS** | Participant Information Sheet |
| **PPI** | Patient and Public Involvement |
| **QA** | Quality Assurance |
| **SMF** | Study Master File |
| **SMG** | Study Management Group |
| **SSC** | Study Steering Committee |
| **SOP** | Standard Operating Procedure |
| **SWAT** | Study Within a Trial |
| **UKCRC** | The United Kingdom Clinical Research Collaboration |
| **USFDA** | The United States Food and Drug Administration  |
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#  1 Synopsis

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| --- | --- |
| **Short title** | Developing core principles for principils using a modified delphi survey |
| **Acronym** | PrinciPIL (Study 1) |
| **Internal ref. no.** | 786 |
| **Funder and ref.** | Medical Research Council (ref MR/V020706/1)  |
| **Study design** | Modified Delphi survey |
| **Study participants** | Stakeholders involved in clinical trials: trial participants, clinicians, ethicists, medico-legal experts, research nurses, and trial managers |
| **Planned sample size** | 50 |
| **Inclusion criteria** | 1. Stakeholders involved in clinical trials
2. Ability and willingness to give informed consent
3. Ability to communicate in English
4. Over 18 years of age
 |
| **Exclusion criteria** | 1. Inability to communicate in English
2. Under 18 years of age
 |
| **Planned study period** | March 2021-November 2021 |
| **Primary objective** | The aim of this study is to understand what information about trial harms and benefits stakeholders consider to be important for PrinciPILs to contain |
| **Observations** | Delphi survey |

# Study Summary & Schema

## Study Schema



## Participant Flow Diagram

## Study Lay Summary

**Full Study Title: Developing Core Principles for PrinciPILs Using Modified Delphi Survey**

Our background research showed that the way in which potential harms of participating in a trial in patient information leaflets can sometimes actually cause harm. In one of our studies, we found that half of the participants in trials who take a placebo treatment (like a sugar pill) report having a negative ‘side effect.’ 1 in 20 of the participants who took a placebo dropped out due to such a ‘side effect.’ There are many reasons for this, including negative expectations. A trial participant might be warned about a possible side effect in a way that caused them to expect, and then actually experience, this side effect. Negative side effects among patients taking placebos were more common in pain-related, cancer, and mental health trials. However, our research has also shown that harms can be presented in a way that is honest, balanced, avoids coercion and at the same time does not induce unnecessary communication-induced harms. In our second study, we looked at 33 Patient Information Leaflets (PILs) and found that the way information about harms was shared did not seem to follow any logical pattern. Most of them had more information about harms than potential benefits, and some did not mention potential benefits at all. We agree with the need to inform patients and avoid coercion. However, our research has also shown that harms can be presented in a way that is honest, balanced, avoids coercion and at the same time does not induce unnecessary communication-induced harms.

Patient representatives and other stakeholders are already involved in designing information leaflets for patients in trials. However, there is currently no guidance *specifically* on how they should include information about potential benefits and harms.

In this study, we will survey 50 stakeholders to understand their views about how the information about trial participation harms and benefits should be communicated. The stakeholders will include patients, research ethics committee members, clinicians, medico-legal experts, regulators, and clinical trial managers. The survey will be conducted online and be completely anonymous. At the end of the study, we will have a meeting with our advisory board to finalise the principles. These principles will then be used to design ‘principled patient information leaflets’ or ‘PrinciPILs’.

##

# Rationale for the Study

Presentation of potential trial participation harms and benefits in PILs varies, with trial benefits sometimes not being mentioned. This can cause information-induced adverse events (‘nocebo effects’). Because guidance regarding the best way to present potential trial participation benefits and harms does not exist, scarce resources are also wasted, with every Principal Investigator (PI) having to negotiate their own method (reinventing the wheel). Our aim is to develop key principles to be considered when sharing information about potential trial benefits and harms within PILs by obtaining stakeholder views. We will obtain participant, clinician, ethicist, medico-legal expert, research nurse, and trial manager views about how to balance information about trial harms and benefits within PILs.

# Study Aims and Outcomes

## Aim of the Study

The aim of this study is to understand what information about trial harms and benefits stakeholders consider to be important for PrinciPILs to contain.

## Primary Outcome

List of key principles to be considered when sharing information about potential trial benefits and harms within PILs.

# Study Design and Setting

## Development of the List of Items for the Delphi (Months 0-3)

We will generate a list of potential information about benefits and harms from three sources that our background research has revealed to be important: 4-6

1. principles and examples from our review of UK PILs; 5
2. extracted principles and example from a random sample of Drug Facts Boxes; 7
3. statements in official guidance about presenting trial benefits and harms in PILs from within the UK (e.g. HRA: <https://bit.ly/303HGg5>) and internationally (e.g. European Medicines Agency (EMA): <https://bit.ly/2MqCPO2>; World Health Organisation (WHO): <https://bit.ly/2U6mx12>; The United States Food and Drug Administration (USFDA): <https://bit.ly/3dvMe2K>).

These will be collated, and the list will be piloted for face validity by our patient and public representatives. The information sources will then be used to generate a comprehensive list of principles about benefits and harms. The co-applicants, supplemented by the PPI representative and advisory group will remove redundancy.

There is currently no standard method for determining sample size calculations for Delphi studies. While 5 to 10 experts are considered adequate for content validation, we will purposefully sample at least 50 people in order to have diverse representation. A purposive sample from each stakeholder group will be identified. Sampling will be conducted within each stakeholder group to provide a balance of participants across the groups in terms of gender, age, and ethnic background.

Having a diverse range of professional backgrounds and expertise will ensure a variety of views. Our facilitators have experience conducting Delphi studies. In addition, the survey component of the Delphi process will be conducted online anonymously. These measures will reduce the risk that any single respondent’s potential biases do not dominate the process or conclusions.

Invitation letters describing the Delphi survey will be sent through the email distribution list with interested parties being asked to complete the Delphi questionnaire, which will be an online questionnaire accessed through an embedded web link in a direct email.

## Delphi Survey: Design

We will use Qualtrics or COMET for the Delphi survey. Participants will be invited to participate by email. If they agree to participate, they be sent an email containing unique participant ID number. Following methods used in a related study, 3 our Delphi survey will begin with a brief introduction of the aim of the study, how the information collected will be used and stored, how the findings will be made available to them and will remind participants of the importance of competing all rounds.  Participants will be asked to tick a box at the start of the survey to confirm that they agree to participate and that they understand that they have a right to withdraw from the study at any time. Participants who do not confirm will be considered as having withdrawn from further participation. Reminder emails will be sent to non-responders at each round.

The questions will also involve examples that are relevant to the trials we have identified in which we will embed SWATs of PrinciPILs. We anticipate that there may not be consensus that there is a ‘one size fits all’ approach to sharing information about potential harms. The way in which information about potential harms is likely to depend on a number of factors including the degree of potential harm (mild versus serious) and the degree of the potential benefit (minimal, moderate, or large). It may nevertheless be possible to stratify the communication methods depending on the degree of risk and benefit.

This project will comply with GCP and CTR SOPs and participants’ confidentiality will be maintained. The online survey tool is GDPR compliant. All data will be kept in line with Cardiff University’s Research Governance Framework Regulations for non-clinical research for no less than end of project + 5 years or at least 2 years post publication. The data will be stored confidentially on password protected servers maintained on the Cardiff University Network and University of Liverpool server during the online survey, and in accordance with the 1998 Data Protection Act and GDPR regulations.

## Delphi Survey: Conduct

**Delphi Round 1**

As defined in other Delphi surveys for developing important principles, participants will be asked to score each of the listed items using the Grading of Recommendations, Assessment, Development and Evaluations (GRADE) scale of 1 to 9. 8 We will annotate the scale so that a score of 1 to 3 is interpreted as having ‘limited importance’, 4 to 6 as ‘important but not critical’ and 7 to 9 as ‘critical’. They will also be given the opportunity to share free text comments where they can provide reasons for their answers, and suggest other features they believe are important. Examples of potential stakeholder responses *might* include: ‘information about likely harms should be presented before information about likely benefits,’ or ‘information about likely harms should be proportional to the anticipated harms.’

We anticipate that the principles are relative to the severity of the potential harms as well as the magnitude of the potential benefits. We will therefore use vignettes (based on real examples) to ask participants whether the way benefits and harms are presented should be different across a variety of magnitudes of potential trial harms and potential trial benefits.

In addition, the stakeholder group will be asked how large a reduction in AEs would be considered clinically important for justifying the use of PrinciPILs.

Descriptive statistics will be used to summarise the results from each round. For each item, the distribution of scores (frequency distribution, the median and interquartile range) will be summarised by stakeholder group alongside the total number of participants who scored the item. Any new additional items listed by participants in round 1 will be reviewed and coded by two members of the study team to ensure they are independent from those listed, with a third reviewer acting as an arbiter if there is disagreement. Participants will be instructed to rate all items on their own merit even if they appear similar. All items will be carried forward to round 2.

Following the completion of round 1, the results will be presented for the research team as the total number of registrations to the website, the number of participants who have completed round 1, the total number of participants in each stakeholder group and the number of respondents as a percentage of those invited by stakeholder group.

Round 2 assumes sufficient numbers respond to round 1 across each of the stakeholder groups. If there are inadequate numbers for one or more stakeholder groups, the Advisory Group will be consulted. For the purposes of this project, inadequate numbers have been predefined by the project team as fewer than 20 in any stakeholder group. The rationale for this lower limit has been informed by a study by Harman et al. who used a lower limit of 10 in any stakeholder group. 9 Those who have not taken part in round 1 (that is, did not score items) will not be invited to participate in further rounds.

**Delphi Round 2**

Round 2 of the Delphi survey will also be presented online. Participants will be presented with feedback (number of respondents, distribution of scores across the 1-9 scale, and collated free text comments). This will include histograms showing the responses by stakeholder group, changes between the round, as well as any modifications of the survey instrument such as deletion, addition or modification of survey items based on previous rounds. Participants will be asked to rescore the item again in light of the scores of others in their randomised group, using the nine- point scale.

The total number of participants invited to participate in round 2 will be recorded and compared to the total number of round 2 responders (and compared for response bias between the two randomised feedback groups). For each item, the distribution of scores will be summarised across stakeholder groups.

If consensus is reached (see ‘Definition of consensus’, below), the Delphi survey will close after two rounds. Otherwise, we will proceed to a third round.

**Delphi Round 3**

If stability is not reached after two rounds, we will conduct a third round of the survey. In the final online round of the Delphi, participants will be presented with the distribution of scores in the same way they were for Round 2 and reminded of their personal score from Round 2. Participants will then be asked to rescore all items and consider whether, and why, they should be included as an important principle.

The total number of participants invited to round 3 will be recorded and compared to the total number of round 3 responders. For the final analysis, for each item, the number of participants who scored the item and the distribution of scores will be summarised, alongside the number of respondents who scored the items across all three rounds. For each item, the proportion of respondents scoring 1 to 3, 4 to 6 and 7 to 9 on the Likert scale will be calculated for each item. Each item will be classified as: ‘consensus in’ (that is, consensus that the item should be included in a core set), ‘consensus out’ (that is, consensus that the item should not be included in a core set) or ‘no consensus’ (that is, items that are equivocal and require further clarification).

## Definition and Attainment of Consensus

We will analyse the open-ended responses by grouping and summarizing similar answers, using response frequencies to assess the closed-ended responses. We will take consensus to be defined as follows:

* **Consensus in (that an item is important)**: agreement of a substantial majority (≥70%) of panellists that an item is of critical importance.
* **Consensus out (that an item is not important)**: agreement of a substantial majority (≥70%) of panellists that an item is of limited importance.
* **No consensus**: Anything else.

The cut-off reflects recommended quality indicators for a Delphi study. 10 Items about which there is no consensus in the face-to-face meeting, with an aim to resolving them or ensuring how to consider the lack of consensus in the eventual PrinciPILs.

## Face to Face Meeting

For the final step of this modified Delphi method, we will convene a face-to-face (if possible) meeting with the co-applicants, and two members from each stakeholder group. The main aim of the meeting will be to determine consensus (in or out) for those items which exhibited no consensus but also to ratify those for which there was agreement in and those.

In advance of the meeting participants will receive: a brief summary of the results of the Delphi survey associated scores, and the analysis to show whether consensus has been reached or not.

The discussion group will be face-to-face if permissible (or a virtual meeting) and will be facilitated by the study team. The discussion will be conducted by CTR and will run from 10am to 3pm. The format and process of the consensus meeting will take account of the potential issues of power and communication and other barriers that may affect participation by some stakeholders. Strategies will be used to minimize the influence of power differentials between different stakeholders during the meeting and provide support for their inclusion, including ensuring good preparation, an enabling environment with strong support for participants, and the use of good facilitation skills.

The items that achieved consensus will be presented briefly and participants asked to voice any disagreement. Items that are considered overlapping will be highlighted and participants asked to consider which should be considered ‘core’. Once these are agreed, they will be written on a white board/flip chart such that they can be referred to/reflected upon throughout the remainder of the process. The focus for the rest of the meeting will be on the items with no consensus. Each item will be presented in turn alongside its definition and scores from individual stakeholder group Delphi responses. Discussion will be welcomed requesting any points of clarification and an opportunity to consider whether the item should be considered as important. At this stage it will also be important to consider whether any of the items being considered are surrogates for any items already listed within those for which there was consensus (in or out). Participants will then be asked to vote (using polleverywhere.com) on whether the item should be included or not. The same voting scale used in the Delphi will be applied i.e. 1-9 where 1-3 = not important, 4-6 = unclear, and 7-9 = important. For an item to be voted in more than 70% of the group have to agree on its inclusion i.e. vote it 7-9. If less than 70% score it 7-9 it will not be included. At the end of the voting process the final items set will be presented to the group.

We will explore reasons for stable non-consensus and take these into account in our PrinciPIL development. For example, if there is disagreement about whether information about benefits should come before information about harms, we might consider using both methods and exploring which was deemed to be more useful in our qualitative interviews.

We will document the discussions during the consensus meeting paying particular attention to any gaps or minority concerns about the list that achieved consensus so as to reflect on any potential limitations. These discussions will also provide further opportunity to hear a refined discussion of the reasoning for regarding some item domains as important. By the end of the consensus meeting, ‘what’ principles to include should have been identified.

## Risk Assessment

A Study Risk Assessment will be completed to identify the potential hazards associated with the study and to assess the likelihood of those hazards occurring and resulting in harm. This risk assessment will consider:

* The known and potential risks and benefits to human subjects
* How the risk will be minimised/managed

Participation in surveys and the discussion makes certain demands on participants. To mitigate against this risk, researchers will be flexible in arranging the discussion and modify plans if required. The surveys can be completed at a time convenient to the participant, within an agreed timescale.

There is a risk (however small) of disclosures of poor practice/negligence or safeguarding issues. Should this occur, the researchers would notify any disclosures to the CI who would discuss this with CTR Quality Assurance team to ensure appropriate corrective action.

# Participant selection

Participants are eligible for the study if they are able to contribute to the aims of the study and if they meet all of the following inclusion criteria and none of the exclusion criteria apply.

## Inclusion Criteria

1. Stakeholders involved in clinical trials
2. Ability and willingness to give informed consent
3. Ability to communicate in English
4. Over 18 years of age

## Exclusion Criteria

1. Inability to communicate in English
2. No access to internet
3. Under 18 years of age

# Participant Identification and Recruitment

## Participant Identification

A group of stakeholders will be identified from the contact lists and networks of co-applicants and PPI representatives and they will be invited to participate in the online Delphi survey. The survey will only be available in English language due to the time-limited nature of the study. Consideration has been given to the representativeness of the stakeholders that will be included and the ability of people across the different groups to engage with the consensus process. Stakeholders will include at least 5 representatives from each of the eight following sources:

1. **Patients and advocates**. Our Patient and Public Involvement (PPI) representative (Jennifer Bostock) will help us identify these from their networks including PainUK and People in Research (NIHR), the James Lind Alliance and from health literacy groups (for example, [www.healthliteracy.org.uk](http://www.healthliteracy.org.uk)). They will also be selected based on experience with one of the conditions in which information induced harm is more likely (cancer, musculoskeletal conditions and mental and behavioural disorders).
2. **Ethics committee chairs**. The PI and co-applicants have contacts at the Health Research Agency (HRA) who have expressed willingness to put us in touch with interested ethics committee chairs.
3. **Industry**. We will identify these with help from our industry partners, including the Association of British Pharmaceutical Industry
4. **Psychologists**. These will be identified by the PI and co-applicants, who have an extensive network of psychologists with relevant expertise.
5. **Research Nurses**. We will identify these via the UK Clinical Research Collaboration (UKCRC) Registered Centre for Trials Research at Cardiff University.
6. **Behavioural scientists**. We will identify these through the PI and co-applicants’ contacts at the UK Society for Behavioural Medicine.
7. **Risk communicators**. These will be identified via the PI’s networks at the Said Business School
8. **Medico-legal experts**. These will be identified through the PI and co-applicants’ as well as the PPI representative’s contacts.

## Informed Consent

Informed consent will be sought in advance via an online consent form as part of the Delphi online survey.

Information provided via the online informed consent form will include:

* Explanation of the purpose of the survey
* Description of all study procedures
* Potential risks and discomforts
* Potential benefits
* Expected duration of participant involvement
* Confidentiality
* Contact details for any comments, questions and/or concerns
* Consent section

The online consent form will also clearly outline that participants have the option to opt out or withdraw at any time point during the data collection phase. They will also make clear that any data collected prior to their withdrawal will be retained and that once the study is being disseminated it may not be possible to withdraw their contribution. Participants will have the right to refuse to participate in the study or to withdraw from the study at any time without giving reasons.

# Withdrawal & Lost to Follow-up

## 8.1 Withdrawal

Participants have the right to withdraw consent for participation in any aspect of the study at any time for any reason or be withdrawn from the study at the discretion of the Chief investigator. Participants will withdraw from the study by contacting a member of the study team. Contact details will be provided in study information. The withdrawal of participant consent shall not affect the study activities already carried out and the use of data collected prior to participant withdrawal. The use of the data collected prior to withdrawal of consent is based on informed consent before its withdrawal.

If a participant initially consents but subsequently withdraws from the study, clear distinction must be made as to what aspect of the study the participant is withdrawing from. These aspects could be:

Partial withdrawal from further data collection (e.g. some of Delphi surveys, discussion)

Complete withdrawal from further data collection

Complete withdrawal of permission to use data already collected

In all instances participants who consent and subsequently withdraw will be requested to complete a withdrawal form or the withdrawal form will be completed on the participant’s behalf by the researcher based on information provided by the participant. A copy of the withdrawal form will be sent to the study manager by email and stored in the Study Master File (SMF). The record of participants will be updated accordingly.

## 8.2 Lost to Follow up

Participants who cease to respond to the Delphi surveys rounds or fail to attend the face-to-face meeting without notifying the study team will be classed as lost to follow up. Every effort will be made to contact these participants, unless they have completely withdrawn from the trial.

# 9 Study Procedures

The expected duration of participant involvement is six months.

* Weeks 1-3: Delphi Survey Round 1 - Participants will be invited by direct email letter to complete anonymous online Delphi questionnaire through web link embedded in email
* Weeks 5-7: Delphi Survey Round 2 - Participants will be presented online with feedback from Round 1 of the Delphi Survey. Participants will be asked to re-score the item again in light of the scores of others in their randomised group. If consensus is reached, the Delphi survey will close after two rounds. Otherwise, we will proceed to a third round.

Consensus: If consensus is reached, the Delphi survey will close after two rounds. Otherwise, we will proceed to a third round.

* Weeks 9-11: Delphi Survey Round 3 - Participants will be presented with the distribution of scores in the same way they were for Round 2 and reminded of their personal score from Round 2. Participants will then be asked to rescore all items and consider whether, and why, they should be included as an important principle.
* Week 12: Face to face meeting - Co-applicants and two members from each stakeholder group will meet to determine consensus (in or out) for those items which exhibited no consensus but also to ratify those for which there was agreement in and those. In advance of the meeting participants will receive: a brief summary of the results of the Delphi survey associated scores, and the analysis to show whether consensus has been reached or not.

# 10 Statistical Considerations

## 10.1 Sample Size

The planned sample size is not derived statistically. While 5 to 10 experts are considered adequate for content validation, we will purposefully sample at least 50 people in order to have diverse representation.

# 11 Analysis

## 11.1 Main Analysis

### 11.1.1 Sub-group & Interim Analysis

Descriptive statistics will be used to summarise the results from each round of the Delphi surveys. For each item, the distribution of scores (frequency distribution, the median and interquartile range) will be summarised by stakeholder group alongside the total number of participants who scored the item. Any new additional items listed by participants in round 1 will be reviewed and coded by two members of the study team to ensure they are independent from those listed, with a third reviewer acting as an arbiter if there is disagreement. Participants will be instructed to rate all items on their own merit even if they appear similar. All items will be carried forward to round 2.

For the final analysis, for each item, the number of participants who scored the item and the distribution of scores will be summarised, alongside the number of respondents who scored the items across all three rounds. For each item, the proportion of respondents scoring 1 to 3, 4 to 6 and 7 to 9 on the Likert scale will be calculated for each item. Each item will be classified as: ‘consensus in’ (that is, consensus that the item should be included in a core set), ‘consensus out’ (that is, consensus that the item should not be included in a core set) or ‘no consensus’ (that is, items that are equivocal and require further clarification).

### 11.2.2 Definition and Attainment of Consensus

We will analyse the open-ended responses by grouping and summarizing similar answers, using response frequencies to assess the closed-ended responses. We will take consensus to be defined as follows:

* **Consensus in (that an item is important)**: agreement of a substantial majority (≥70%) of panellists that an item is of critical importance.
* **Consensus out (that an item is not important)**: agreement of a substantial majority (≥70%) of panellists that an item is of limited importance.
* **No consensus**: Anything else.

The cut-off reflects recommended quality indicators for a Delphi study. 10

Face to face meeting: Participants will be asked to vote (using polleverywhere.com) on whether the item should be included or not. The same voting scale used in the Delphi will be applied i.e. 1-9 where 1-3 = not important, 4-6 = unclear, and 7-9 = important. For an item to be voted in more than 70% of the group have to agree on its inclusion i.e. vote it 7-9. If less than 70% score it 7-9 it will not be included. At the end of the voting process the final items set will be presented to the group.

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## 11.2 Qualitative Analysis

We will explore reasons for stable non-consensus and take these into account in our PrinciPIL development. For example, if there is disagreement about whether information about benefits should come before information about harms, we might consider using both methods. We will document the discussions during the consensus meeting paying particular attention to any gaps or minority concerns about the list that achieved consensus so as to reflect on any potential limitations. These discussions will also provide further opportunity to hear a refined discussion of the reasoning for regarding some item domains as important. By the end of the consensus meeting, ‘what’ principles to include should have been identified.

# 12 Data Management

All procedures for data storage, processing and management will comply with the CTR Standard Operating Procedures (as the lead site), CPRD & Public Health Wales data sharing agreements and the General Data Protection Regulation 2016.

The face-to-face discussion will be transcribed by a commercial transcription service which will be required to sign a Cardiff University confidentiality agreement.

A study One Drive folder will be set up which will be managed from the CTR by the Study Manager and will allow all study members to access and upload project documents and anonymised data. One Drive is of a sufficient standard for UK Data Protection legislation 2018, and is supported by Cardiff University. Team members will be able to access material at any time, although permissions for restricted access will be set per folder or document so that only relevant material would be accessed. Permissions and restrictions will be managed by the study manager.

Consent forms, contact forms and transcripts of discussions will be stored on password-protected computers in CTR. Identifiable data (consent, contacts forms) will be stored separately from data. Participants will be assigned an identifier and a consent log will be used on the study One Drive to keep a record of participants and will link identifiers to participants. This will be maintained and managed by the CI and the study manager.

Interviews will be recorded through Microsoft Teams and an audio-recorder and saved on secure Cardiff University servers. Files will be password protected, and accessible only to relevant members of the research. Recordings will be transcribed and anonymised in line with CTR Standard Operating Procedures. All essential documents generated by the study will be kept in the SMF and/or on the electronic SMF and managed by the study manager. Cardiff University demonstrates compliance with current information governance requirements as set out in the Department of Health Policy with an information governance toolkit score valid from 1 April 2018 of 88%.

Group discussion data: Audio-recording of deliberative face-to-face meeting, recorded and audio file transcribed. The software and file formats used throughout will allow for data sharing (if appropriate) and will ensure the data is valid in the long term.

**Quantitative data:** Data will be entered/stored/retrieved in Medidata Rave; a fully validated ERES / GCP compliant, secure, web-based interface electronic data capture (EDC) system.

# 13 End of Study Definition

The end of the study is defined as the date of final data capture to meet the study endpoints. In this case end of study is defined as the end of the consensus meeting, when ‘what’ principles to include in the PILs should have been identified.

# 14 Archiving

The SMF containing essential documents will be archived at an approved external storage facility for a minimum of 5 years (data sharing agreements will be maintained to allow for the routine data to be archived for this duration). The CTR will archive the SMF on behalf of the Sponsor. Essential documents pertaining to the study shall not be destroyed without permission from the Sponsor.

# 15 Regulatory Considerations

## 15.1 Ethical and Governance Approval

Ethical approval will be obtained from Cardiff University School of Medicine Research Ethics Committee prior to commencing the survey.

## 15.2 Data Protection

The CTR will act to preserve participant confidentiality and will not disclose or reproduce any information by which participants could be identified, except where specific consent is obtained. Data will be stored in a secure manner and will be registered in accordance with the General Data Protection Regulation 2016 and the UK Data Protection legislation 2018.

## 15.3 Indemnity

Cardiff University shall indemnify the site against claims arising from the negligent acts and/or omissions of Cardiff University or its employees in connection with the study.

## 15.4 Funding

This study is funded by the Medical Research Council.

# 16 Study Management

## 16.1 Project Management

The study will be fully co-ordinated by the UK Clinical Research Collaboration registered CTR, Cardiff University. The study will be managed according to the standard operating procedures of CTR and contracts established between Cardiff University and the institutions of the co-applicants. The lead applicant will assume overall scientific and financial responsibility for the study and the study manager will be responsible for day-to-day overview of the study.

## 16.2 Study Management Group (SMG)

A Study Management Group will comprise the lead and co-applicants, two Research Associates based at Cardiff University and will meet at least quarterly to regularly review study milestones.

## 16.3 Project Team (PT)

The project team will comprise Dr Jeremy Howick (CI), two Research Associates and a study administrator based at Cardiff University. The project team will meet weekly for the duration of the study to review progress and ensure the study is delivered within time and budget.

# 17 Publication Policy

The results of this study will be written up for a peer-reviewed publication, which will be authorized by the Study Management Group.

Our project impacts will be achieved through active dissemination and exploitation of our findings. The first main impact is: **economic impact through reducing waste and improving trial efficiency**. Currently, individual research ethics committees make decisions about how to present information about potential benefits and harms on an ad hoc basis, which involves (to some degree) re-inventing the wheel. Our guidance will save time by providing principles and examples for how to do this.

Improving recruitment and retention rates will make high quality and adequately powered trials more efficient. Rationalizing and making the way in which potential trial benefits and harms are presented within PILs transparent will reduce time PIs think about how to present potential benefits and harms, reducing research waste. PrinciPILs will thus make UK industry more competitive. The second main impact is: **enhancing quality of life by reducing harm**. PrinciPILs may minimise information- induced harm, improving trial participant quality of life.

Our findings, guidelines and resource on the effective use of PrinciPILs will be disseminated to policymakers, commissioners and providers of research, applicable in the context of local delivery systems. These will include governments, commissioning groups, Royal Colleges, ethics committees, health boards and trials units, UK CRC CTUs as soon as is practicable. Co-applicants are well positioned within their networks to identify the most effective means of dissemination to these groups. Our public contributors will play a leading role in ensuring dissemination to the wider public in the interests of accountability and in keeping with the principles of co-production. The dissemination strategy includes the following elements:

**1. Communication with reporting health organisations**: We will summarise our findings for dissemination to NHS organisations, exploring strategies for dissemination with the advisory board and other senior advisors, consisting of senior policy and operational representatives from NIHR, NET SCC and others.

**2. Media**: Applicants will use their networks to publicise implications for practice. We will identify messages suitable for national and local television, radio and press coverage and via social media. We will publicise findings to interested members of the public, e.g. through the existing participants in Biobank, Health Wise Wales, National Voices, Health & Social Care Alliance of Alliances.

**3. Patient and public involvement/engagement**. We have involved members of the public from the inception of this project. Our PPI representative has extensive public engagement experience, including with the HRA. Additionally, we have a public engagement activity planned with the Clod Ensemble (see ‘Project Partners’).

**4. Peer-reviewed publications**: Our team has demonstrable success at producing high-profile academic outputs including journal publications with major impact in subject areas relevant to this proposed project. A final MRC report will be written giving a full account of methodology and its findings.

**5. Education and training:** We will plan educational events in collaboration with funders and trials units and a learning module for early career researchers, including how to use the resource, potentially hosted via Innovate UK, NIHR and NETSCC.

**6. Creating a framework for generalization**: We will communicate results when it becomes clear that the results have stabilized or generalized to another context.

**7. Conferences**: We will use our advisory group meetings to cascade the evidence and resource to other groups, including further relevant meetings / conferences. While some aspects of this research are NHS specific, our approach will identify internationally generalizable findings. Our co-applicants include several members experienced in health policy or service delivery, and who are often invited to present at international (including industry) conferences.

**Project Partners (for helping with dissemination)**

Several individuals/organisations have provided letters of support. Professor Badgett is the main developer of OpenMetaAnalysis and will support us to develop the infrastructure for testing ours and future PrinciPIL Studies Within a Trial (SWATs). The Clod Ensemble will support a public engagement activity. The Association of the British Pharmaceutical Industry will help disseminate key findings through their networks. Dr. Amy Price (British Medical Journal (BMJ) Group) will assist with patient and public engagement.

# 18 Milestones

By end of month 1: List of items for the Delphi developed

By end of month 2: Delphi Round 1 completed

By end of month 3: Delphi Round 2 completed

By end of month 4: Delphi Round 3 completed/Definition and attainment of consensus

By end of month 5: Face-to-face discussion held and ‘what’ principles to include in the PrinciPILs identified

# 19 References

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