Centre for Trials Research

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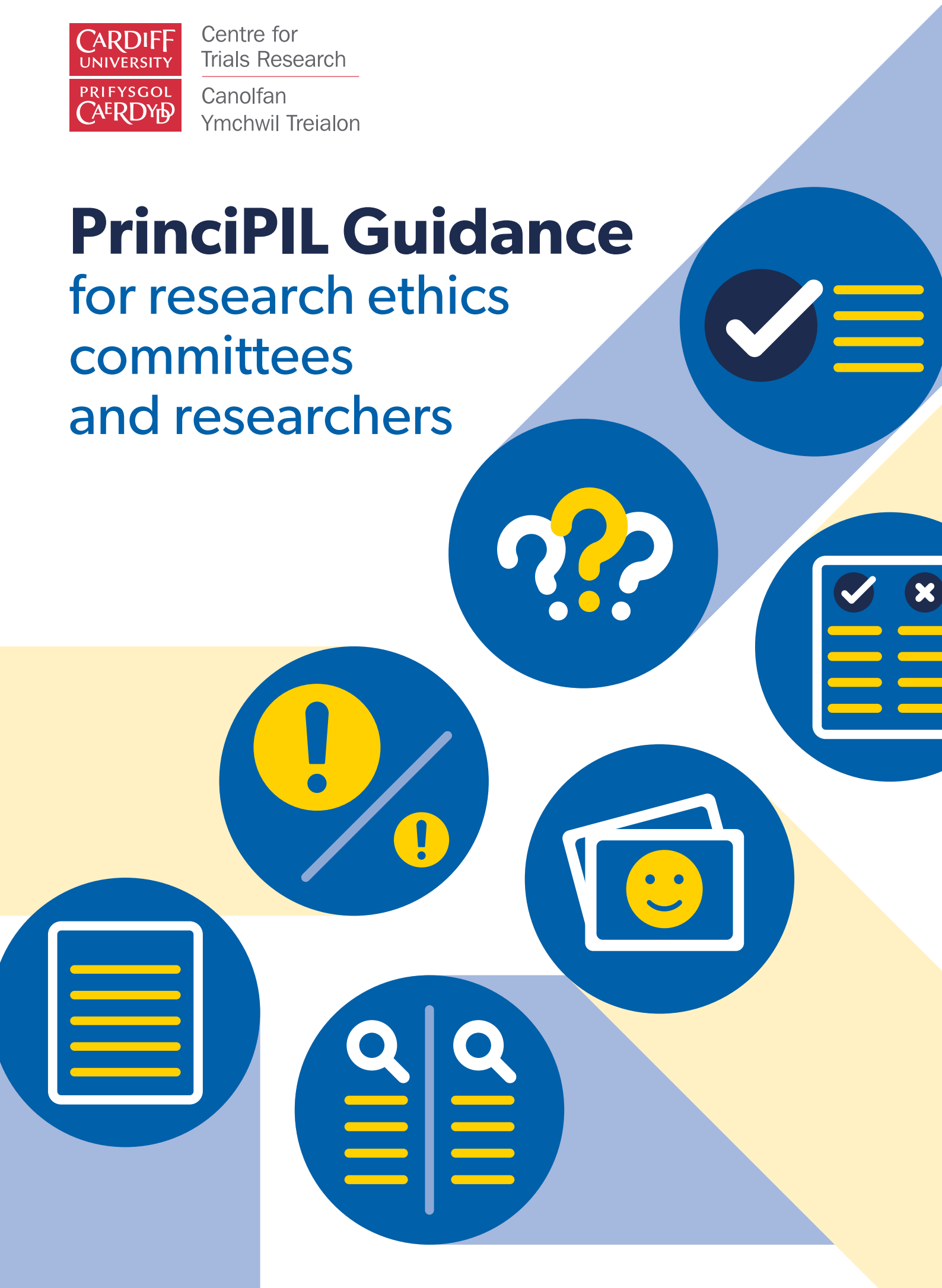
PrinciPIL Guidance

for research ethics committees and researchers



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PrinciPIL Guidance for research ethics committees and researchers
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ISBN: 978-1-3999-5432-7

Quick Guide for Research Ethics Committees

Ethics committees can use the list below as a checklist.
Background research that generated the principles is described on page 4.

All potential harms should be listed. **1**

The harms should be separated into serious (life-threatening, causing permanent damage) and less serious (like a mild headache that goes away quickly). **2**

The fact that not all potential harms are known needs to be clear. Also, sometimes, harms are discovered after the trial begins. **3**

All potential benefits of the intervention should be listed. **4**

Potential benefits and harms of a clinical trial need to be compared with what happens if the participant does not take part in the trial. **5**

Suitable visual representations are recommended where appropriate to describe potential intervention benefits and harms, such as pictograms of faces. **6**

Information about potential benefits and harms should not be presented apart by one or more pages. **7**

Research underpinning the principles

The principles were developed as part of an MRC funded project. The research included a rigorous modified Delphi process with over 200 stakeholders including patients and public representatives, research ethics committee members, industry representatives, medico-legal experts, psychologists, and trial managers. The results of the development work was published in *Trials* in 2022.[1] We have started a research project to clarify the ethical requirement to mention potential benefits.[2-5]

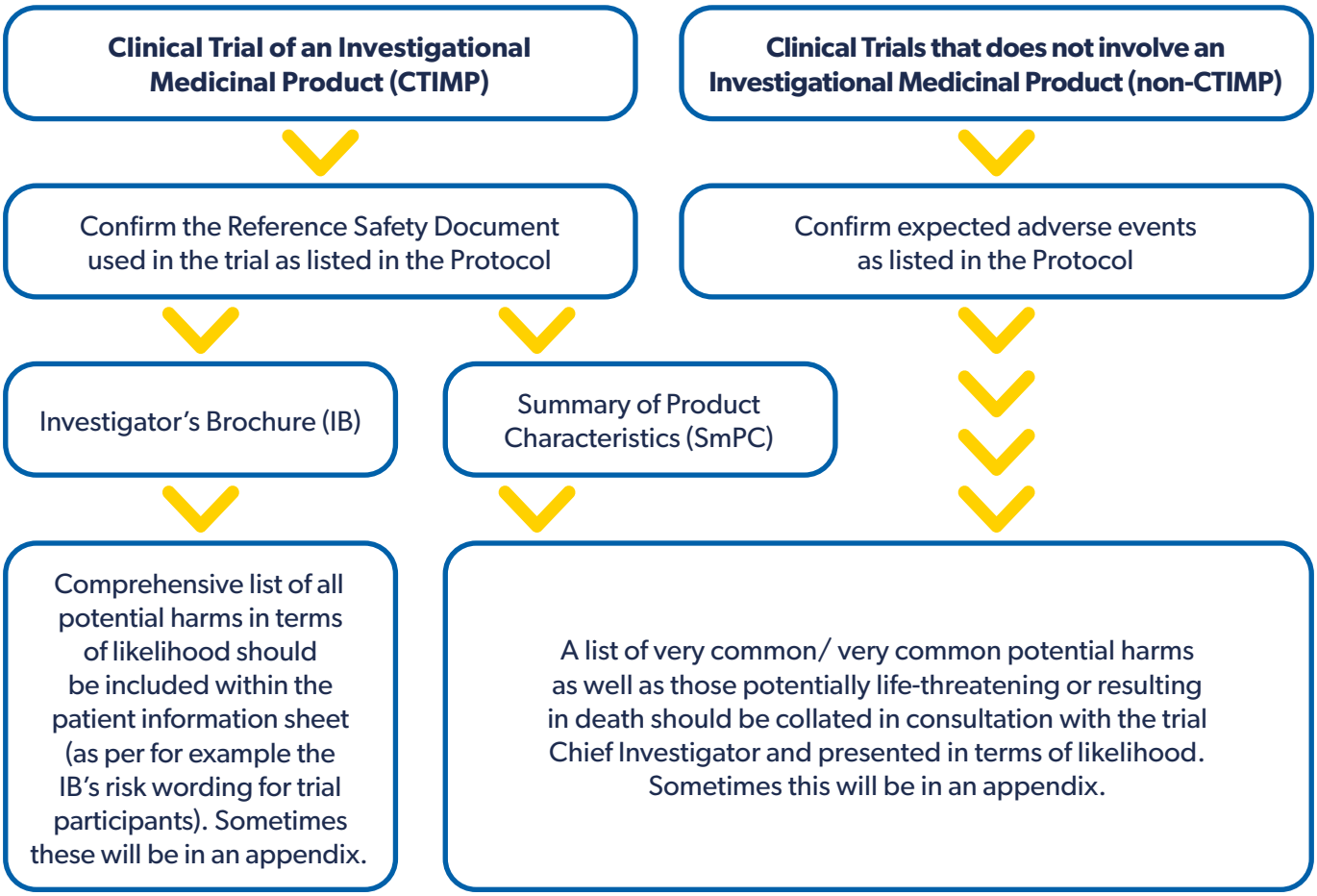
Short video about PrinciPILs

Guidance for researchers who are designing PILs

Principle 1

All potential harms should be listed. *This includes common and rare known and potential harms as well as indirect harms (for example to conceiving a child, being pregnant or breastfeeding).*

The following chart might be helpful when generation the list of potential harms:



Where information is available about potential harms likelihood, the frequency rating developed by the European Medicines Agency can be applied:[6]

- Very common (≥ 1/10)
- Common (≥ 1/100 to ≤ 1/10)
- Uncommon (≥ 1/1,000 to ≤ 1/100)
- Rare (≥ 1/10,000 to ≤ 1/1,000)
- Very rare (≤ 1/10,000)
- Not known (cannot be estimated from the available data)

Principle 2

The harms should be separated into serious (life-threatening, causing permanent damage) and less serious (like a mild headache that goes away quickly)

The separation of potential harms into serious (or common) and less serious (or common) needs to be done in a way that is evidence-based. If less serious and less common harms are put in an appendix, it is important that potential trial participants have seen them and are aware of them (this can be done as part of the informed consent conversation between the person seeking consent and the potential participant).

A distinction should be made between the harms associated with standard clinical care, the harms of the intervention and the comparator being studied and any harms to potential participants with a specific condition.

All potential harms that could result in death must be itemized. For CTIMPs where IMP is subject to additional monitoring, these potential harms should be highlighted.

Principle 3

The fact that not all potential harms are known needs to be clear.

The following statement or similar should accompany the list of potential harms:

> *"Not all potential harms of trial interventions are known and sometimes we get new information about the intervention being studied. If this happens, the research team will contact you and ask if you wish to continue in the trial."*

Principle 4

All potential benefits of the intervention should be listed

The list of potential direct benefits to trial participants should be collated in collaboration with the clinicians and patient representatives on the trial team, taking great care to ensure clarity that these are potential, not guaranteed, benefits.

Potential benefits need to be evidence-based, they cannot be exaggerated, and should be presented objectively in a similar way to potential harms. It is coercive to exaggerate benefits.

Statements of indirect benefits resulting from trial participation such as being seen more often and/or feeling more supported because of involvement in the research etc. should be considered as well as a statement of likely future benefits to others with a similar condition, rather than for study participants themselves, as a result of research discovery.

Contrary to what is sometimes asserted, it is not illegal or against regulations to mention potential benefits, and there is growing consensus that mentioning potential benefits is an ethical requirement.[7]

Principle 5

Potential benefits and harms of a clinical trial need to be compared with what happens if the participant does not take part in the trial.

A clear statement of what would happen to the patient if they did not take part in the trial should precede the description of potential benefits and harms, as in:

> *"If you choose to not take part in the trial, then you will receive [description of what will happen if the potential participant does not take part]."*

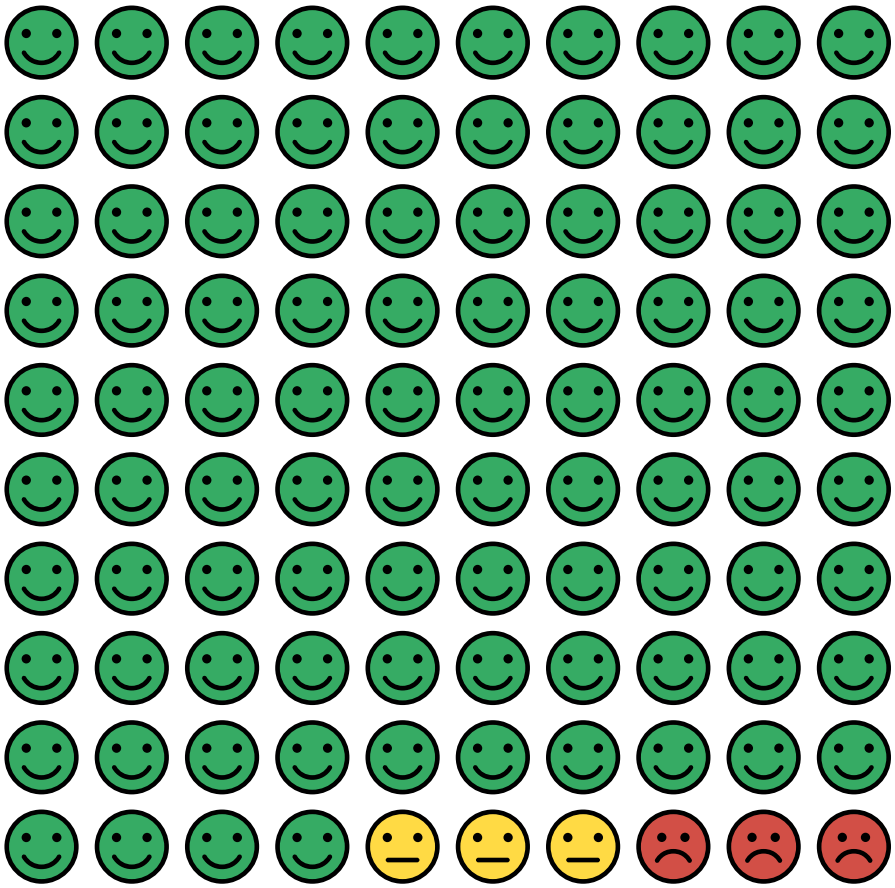
Principle 6

Suitable visual representations are recommended where appropriate to describe potential intervention benefits and harms, such as pictograms of faces

The suitability and content of visual representations is dependent on the trial, the potential trial participants, and the nature of the potential harms and benefits.

Principle 6 Example 1

Happy / sad faces have been used to visually illustrate the chances of a bad outcome arising:[8]



Key

- Good outcome
- Bad outcome
- Better with treatment

Principle 6 Example 2

Identifying suitable visual representations of harm is made more difficult by the underlying problem with conveying harms in general.[9] It is, however, always possible to present the list of harms and benefits in several ways, which allows readers to choose the one they prefer.

What are the potential benefits of taking part?

There are several 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 [medication]:

- ✓ **You will be able to use highly effective alternatives to [medication]**
- ✓ **You may get better faster**
- ✓ **You may need fewer painkillers**
- ✓ **You will lower your chances of developing resistance to [medication]**
- ✓ **Your medical record will be updated**

Regardless of which trial group you are in, and whether or not testing confirms that you are allergic:

- ✓ **The study will increase access to testing and may reduce resistance by reducing the amount of [medication] prescribed and by improving the types of [medication] prescribed by GPs.**

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

The intervention performed in this trial is the same as the testing routinely carried out in the NHS. Also, this testing is safe and severe reactions are rare. For example, in a trial of 1018 tests, five patients (0.5% of patients) had severe reactions. Most of the reactions are mild:

- ✓ **Red rash, with or without blistering or itching**
- ✓ **Nausea**
- ✓ **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 four to six 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.

Principle 7

Information about potential benefits and harms should not be presented apart by one or more pages

Where feasible, the information about potential harms and benefits should be presented on the same page (see above for example).

Incorporating the 7 principles into an existing standard operating procedure (SOP)

The 7 principles can be easily incorporated into an existing standard operation procedure that describes what to write about potential benefits and harms of trial interventions. The easiest way to do this is to add the 7 principles as a checklist (see Guidance for Research Ethics Committees).

A note about communicating risk

There are various ways to communicate harms with patients, and substantial evidence that many patients do not (fully) understand harms, no matter how they are communicated.[9] Addressing the challenge of how to communicate harms with patients is therefore beyond the scope of this guidance. Nonetheless, we believe that our process, which includes facilitating a comparison of potential harms and potential benefits, as well as using plain English, is a useful contribution to the literature on communicating harms. As more evidence regarding effective harm presentation becomes available, these methods can be used when following our principles.

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