

Applying a proportionate approach to the process of seeking consent

HRA Guidance

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1. Introduction

1.1. The Health Research Authority (HRA)

The HRA exists to promote and protect the interests of patients and the public in health research. We strive, with partners, to make sure the UK is a great place for health research. Recognising that many members of the public want the opportunity to participate in research, we aim to ensure that health research involving them is ethically reviewed and approved, that they are provided with the information that they need to help them decide whether they wish to take part, and that their opportunity to do so is maximised by simplifying the processes by which high quality research is assessed. In doing this, we will help to build both public confidence and participation in health research, and so improve the nation's health.

1.2. Scope of this guidance

This guidance emphasises and clarifies the application of the principle of proportionality to the provision of information to potential research participants (or, where appropriate, their legal proxies, consultees or other legal representatives) for the purpose of seeking their consent (or advice in the case of consultees) in accordance with applicable UK-wide legal requirements. It describes ways in which participant information sheets (PIS) can be made more accessible for all types of research. In particular, this guidance focuses on the taking of a proportionate approach in clinical trials including pragmatic trials¹ but also addresses how participant information sheets might be simplified or layered in more complex research.

Whilst the main focus of this guidance is on the provision of information in clinical trials of medicinal products (CTIMPs), it may also be applied to clinical trials of devices and other types of interventional and non-interventional research.

This guidance does not seek to address the issues surrounding research undertaken in an emergency context.

This document is guidance and does not constitute a legal interpretation of the requirements regarding the written information to be given, and the procedure to be followed, for the purpose of obtaining informed consent for participation in a clinical trial as set down within the EU Clinical Trials Directive and the Medicines for Human Use (Clinical Trials) Regulations (SI 2004 1031), as amended. It does, however, reflect the expectations of the Health Research Authority with respect to the provision of information to potential participants/legal representatives/consultees and the seeking of their consent/advice for research in a proportionate manner.

This guidance should be read in conjunction with the HRA's existing 'Consent and Participant Information Sheet Preparation Guidance'² which provides more detailed information on consent, and how to prepare documents to support this process including provision of information in research involving vulnerable groups.

¹ Pragmatic trials (also referred to as 'simple trials', 'comparative effectiveness trials', 'non-Interventional trials' or 'low-intervention trials') do not normally involve any extra interventions beyond those required as part of the patient's routine care and do not withhold effective treatment; rather they compare the effects of accepted or licensed interventions/therapies in the context of current clinical practice.

² <http://www.hra.nhs.uk/resources/before-you-apply/consent-and-participation/consent-and-participant-information/>

2. Guidance

2.1. Applying proportionality to seeking consent

Seeking informed consent is central to the conduct of ethical research and, wherever possible and appropriate, potential research participants should be provided with the information they need to help them decide whether they wish to take part in research or not. Seeking informed consent properly respects a person's right to determine what happens to them.

However, it has been suggested that the requirement and procedures for seeking that consent can sometimes be applied too rigidly and with too little sensitivity to the values that are at stake in connection with different kinds of research protocols³. Others have suggested that the seeking of consent has become either "routinised", posing a threat to the protection of personal autonomy⁴; "cruel"⁵ or a "ritual" hindering valuable research⁶. Furthermore, participant information sheets are often too long and complex and their length and complexity is increasing. Lengthy, complex information sheets covering every minor detail of the research may protect the researcher and sponsor against litigation but they do not necessarily facilitate the genuine understanding and consent of potential participants⁷ nor facilitate recruitment. Excessively long participant information sheets can also overburden the health care professional (HCP) seeking consent and may even deter some health care professionals from taking part in the recruitment process at all.

A proportionate approach to seeking consent, i.e. adopting procedures commensurate with the balance of risk and benefits, should always be adopted so that potential participants are not overwhelmed by unnecessarily lengthy, complex and inaccessible information sheets but instead are provided with succinct, relevant, truthful information in a user-friendly manner that better promotes their autonomy. Indeed, in many cases it will be the *verbal* exchange of information during the discussion of the proposed research that will be crucial in facilitating the potential participant's decision^{8,9,10}, but this can often be neglected if undue emphasis is placed on the *written* materials to be provided.

The emphasis on proportionality is not new. Indeed, the HRA has long recognised the importance of a proportionate approach in both the regulation and the conduct of research. Both researchers and Research Ethics Committees (RECs) should always consider whether the proposed research procedures, including the information provided to potential participants and how it is presented, are necessary, justified and proportionate.

The methods and procedures used to seek informed consent and the level of information provided should be *proportionate* to:

- **The nature and the complexity of the research;**
- **The risks, burdens and potential benefits (*to the participants and/or society*);and**
- **The ethical issues at stake.**

³ Hansson MO. Balancing the quality of consent. J Med Ethics 1998;24:182–7.

⁴ Ploug T, Holm S. Informed consent and routinisation. Journal of Medical Ethics 2012;39:214-218.

⁵ Tobias J, Souhami R. Fully informed consent can be needlessly cruel. BMJ 1993;307:1199-1201.

⁶ Roberts I, Prieto-Merino D, Shakur H et al. Effect of consent rituals on mortality in emergency care research. The Lancet 2011;377:1071-1072.

⁷ O'Neill O. Some limits of informed consent. Journal of Medical Ethics 2003;29:4-7.

⁸ Flory J, Emanuel E (2004) Interventions to improve research participants' understanding in informed consent for research: a systematic review. JAMA; 292(13): 1593-1601.

⁹ Nishimura A, Carey J, Erwin P et al. Improving understanding in the research informed consent process: a systematic review of 54 interventions tested in randomized control trials. BMC Medical Ethics 2013;14:28

¹⁰ Kirkby, H. M., Calvert, M., McManus, R. J., & Draper, H. (2013). Informing potential participants about research: Observational study with an embedded randomized controlled trial. PLoS One, 8(10), e76435

For example, the participant information sheet and consent form used to seek consent for a low-risk Phase 4 trial of licensed products might be expected to take a different form to that used to recruit to a complex early phase drug trial.

The closer the research is to standard clinical practice, the less need there is to provide patients and service users with detailed and lengthy information about the research. By the same token, the more research deviates from established clinical practice or otherwise detrimentally affects the balance between the anticipated risks and benefits, the greater the need to cover a wide range of information in detail and to convey that complexity in a way that potential participants can understand.

2.2. Providing information to potential participants

The common law¹¹ requires that participants be informed, in **broad terms**, of the **nature and purpose**¹² of the research and **the material risks, benefits and reasonable alternatives**¹³.

In the case of drug trials all participants must have been informed of **the nature, significance, implications and risks of the trial**¹⁴.

It is possible to provide this information in a succinct way which provides the core detail that participants need to know in a meaningful fashion without overloading them. This requires paying attention to the way the information is conveyed, using language that most people can understand and considering the layout and format including the use of visuals where this aids explanation. We strongly encourage testing participant information with an appropriate group of people (patient groups and/or other members of the public)¹⁵ to ensure that it truly meets their needs. Medical writers with experience of writing in plain language for the public may also be helpful.

Not all of the information provided in traditional, lengthy information sheets will always need to be provided to participants at the outset when initially seeking their participation. For example, information regarding the practical aspects of research participation such as specific timing of visits, payment of travel expenses, confidentiality, indemnity, withdrawal procedures, complaints procedures, who has reviewed the study etc. might not always be necessary up front and may be provided separately from the core information relating to the nature, significance, implications and risks of the trial.

Potential participants would need to be provided with access to this 'practical' information where it has implications for whether they would want to participate or not in the research e.g. abstinence requirements or significant drug interactions (and they must indicate that they have been provided with the information and agree to the arrangements before they are enrolled in the study). However, for some studies this information may often serve to confuse rather than promote genuine understanding where presented as part of an excessively lengthy information sheet.

In some cases, such as pragmatic trials of existing licensed treatments, there will not be any extra visits nor payment of travel expenses and so many of the items traditionally included in the PIS will not be relevant and may be omitted. It will often be possible to provide all of the necessary information required for a pragmatic trial in a single, short participant information sheet supported by the verbal information provided during the interview with the HCP seeking

¹¹ Law developed by judges through decisions of courts and similar tribunals, as opposed to statutes adopted through the legislative process or regulations.

¹² Chatterton v Gerson [1981] 1 All ER 257

¹³ Montgomery v Lanarkshire Health Board [2015] UKSC 11

¹⁴ The Medicines for Human Use (Clinical Trials) Regulations 2004

¹⁵ You do not need to obtain NHS Research Ethics Committee (REC) approval to test your information sheet with patients or other groups

consent e.g. highlighting of potential adverse reactions and interactions related to the intervention (which, in the case of licensed drugs would also be detailed in the Patient Information Leaflet (PIL) supplied with the medicine pack).

Examples of well-written participant information sheets are available on the HRA website¹⁶. The MRC Clinical Trial Unit at University College London (UCL) have also developed guidance (including real world examples) and a PIS template, based on research evidence, for writing clear and easy to understand information for use in clinical trials. These can be found on the UCL website¹⁷.

2.2.1. Providing information to potential participants: a layered approach

In order for consent to be valid it must be:

- Given freely (with no undue influence)
- By a person with the necessary mental capacity
- Who has been adequately informed

Anyone asked to give their consent to taking part in a research study should:

- neither be coerced nor deceived (and can judge that they are not coerced or deceived);
- not be overwhelmed with information but able to control the amount of information they receive; and
- have the opportunity to withdraw consent previously given.¹⁸

One way to avoid overwhelming potential participants with lengthy and complicated participant information sheets is to provide them with accurate and relevant information to support genuinely informed consent using a 'layered' or 'tiered' approach¹⁹. This layered approach is supported by the HRA and can be applied to a variety of research, not just pragmatic trials.

This 'layered' approach involves providing:

- potential participants initially with a short summary including sufficient, but brief, information (using any appropriate format) needed to decide whether or not to take part in the research;
- user-friendly methods of access to further, more detailed information (e.g. additional paper information sheets, and/or online information) presented in one or more additional layers (but not provided upfront). The primary information should clearly explain how this further information may be accessed.

In this way potential participants control the amount of information they access and can do so in the knowledge that more comprehensive information, is available to them to refer to at any time, before, during and after their participation. This approach is currently used in a wide variety of research methods but may be particularly useful in conveying information about complex clinical trials.

¹⁶ <http://www.hra.nhs.uk/resources/before-you-apply/consent-and-participation/consent-and-participant-information>

¹⁷ http://www.ctu.mrc.ac.uk/resources/patient_involvement/

¹⁸ O'Neill O. Some limits of informed consent. *Journal of Medical Ethics* 2003;29:4-7.

¹⁹ Antoniou E, Draper H, Reed K, Burls A, Southwood T et al. (2011) An empirical study on the preferred size of the participant information sheet in research. *J Med Ethics*; 37: 559-562.

2.2.2. Providing information to potential participants: Use of multimedia

Text-based information on paper will not always be the best format to use for the provision of information to support seeking consent. Other media or non-text-based approaches may often be more appropriate e.g. videos, cartoons, animations, infographic cards, flipcharts, brochures and audio may all be used as patient-friendly introductions to complement, or replace, the traditional paper information sheet. Often the most important factor for potential participants will be the verbal conversation between one or more members of the research team and the potential participant.

It is NOT a legal requirement to provide *written* information for any research trial but is normally considered best practice and advisable to do so. It is important that potential participants are provided with a portable copy of the information e.g. a paper copy (or alternatively, have 'anywhere/anytime' access to the study information online via computers/tablets/smartphones etc. in a form that can be downloaded) in order to both reach an informed decision and have something to refer to during the research to refresh their memory or consult if they have concerns.

Whilst the most practical method for supplying *portable* information will often be paper-based increasingly people expect and want information to be available online. It is acceptable to use online text or multimedia material as the primary means of informing potential participants provided that, where necessary, alternative methods of information provision are available for people who are unable or unwilling to access the internet or engage with multimedia. Paper-based information, which mirrors the multimedia/online information provided, may also be used as a backup where this is requested by the potential participant. The method of information provision used in any study should always take into account the visual or other accessibility needs of the specific group(s) being recruited.

It is important to remember that effective informing is not just about the *provision* of information it also requires ensuring that potential participants have *understood* that information. Interactive questioning of potential participants within the consent process can aid their understanding of the information presented and also highlight areas that potential participants could misunderstand without appearing condescending.

2.3. Time to consider participation

There are no definitive guidelines or legislation regarding the appropriate amount of time (or minimum amount of time) that potential participants should be allowed in order to consider whether to take part in research or not. A proportionate approach (in a non-urgent scenario²⁰) means that for more complex or burdensome studies a longer time may need to be provided for potential participants to consider their decision than that provided for simpler studies involving lower risks. Whilst there may be time constraints imposed by the nature of the research, potential participants should, where possible, be given as long as they need to consider their participation without feeling under pressure.

For research involving only minimal risks and/or little deviation from normal/standard clinical practice, such as pragmatic trials, it may be reasonable to accept a decision taken at the time of approach provided that:

²⁰ This guidance does not address the issues surrounding research undertaken in an emergency context which presents its own set of challenges in terms of providing information about the research and obtaining consent. Further guidance on this is available at: <http://www.hra-decisiontools.org.uk/consent/principles-emergency.html> (HRA Consent and Participant Information Sheet Preparation Guidance - Principles of consent: Emergency research)

- the potential participant is willing to make a decision at that time (i.e. following provision of all relevant information and an interview regarding the trial);
- the potential participant explicitly indicates when giving their consent that they have been provided with that information.

A proportionate approach should be adopted in which the time allowed to make a decision is adapted to the needs of the specific person being approached to take part. The following factors will influence the appropriate time required for potential participants to consider giving consent and should be taken into consideration:

- **The type of research involved.** The more complex or interventional the study the longer time that may be needed for the potential participant to consider taking part.
- **The setting of the research.** In some types of research an immediate decision (whether this is taken by the participant or their legal representative) may be necessary e.g. research in an A&E department requiring an immediate intervention whilst in others the need to allow more time to consent will be paramount particularly where the research involves a vulnerable group or patients who had just been given bad news about their health.
- **The views, convenience and welfare of participants.** Consideration should be given to an individual's right to decide for themselves how long they require to reach a decision (including giving immediate consent). Consideration should also be given to the treatment needs of participants as well as their desire to discuss the research with their family or others.

In some cases, where an intervention is required urgently or the nature of the research will not allow for a decision to be made at a later time, the potential participant may need to be excluded from the trial if they require more time than is available to make a decision.

- **Potential participants should not feel under pressure or coerced into taking part.** Consideration should be given to who is taking consent and the nature of their relationship with the potential participant.
- **The level of understanding of the participants.** This can be influenced both by the complexity of the study (including the complexity of the information provided) and the group of participants to be recruited.
- **The potential for harm and/or benefit.** This should include consideration of the risks involved in treatment delay and possible benefits.
- **Other factors:** e.g. when screening procedures for the study will take place; the possibility that allowing a long time for people to reach a decision may imply that the research is more involved, risky or important than it actually is.

2.4. Proportionality in Clinical Trials of Investigational Medicinal Products (CTIMPs)

The current regulatory framework in the UK allows for a range of risk-adapted approaches that may simplify the processes for initiating and conducting some clinical trials including the methods used for seeking informed consent. The MHRA have published "[Risk-adapted Approaches to the Management of Clinical Trials of Investigational Medicinal Products](#)" which sets out a simple three-level risk categorisation based on the marketing status of the Investigational Medicinal Product (IMP) and standard medical care:

Trial Categories based upon the potential risk associated with the IMP	Examples of types of clinical trials
Type A: no higher than that of standard medical care	Trials involving medicinal products licensed in any EU Member State if: <ul style="list-style-type: none"> • they relate to the licensed range of indications, dosage and form, or • they involve off-label use (such as in paediatrics and in oncology etc.) if this off-label use is established practice and supported by sufficient published evidence and/or guidelines
Type B: somewhat higher than that of standard medical care	Trials involving medicinal products licensed in any EU Member State if: <ul style="list-style-type: none"> • such products are used for a new indication (different patient population/disease group) or • substantial dosage modifications are made for the licensed indication or • if they are used in combinations for which interactions are suspected Trials involving medicinal products not licensed in any EU Member State if <ul style="list-style-type: none"> • the active substance is part of a medicinal product licensed in the EU <p>(A grading of TYPE A may be justified if there is extensive clinical experience with the product and no reason to suspect a different safety profile in the trial population)</p>
Type C: markedly higher than that of standard medical care	Trials involving a medicinal product not licensed in any EU Member State <p>(A grading other than TYPE C may be justified if there is extensive class data or pre-clinical and clinical evidence)</p>

(Table adapted from [ADAMON](#) paper, excluding non-pharmacological interventions²¹)

Using this simple categorisation it is possible to identify lower risk clinical trials, where simplification is possible (e.g. lower risk (Type A) trials such as pragmatic trials), resulting in a more proportionate approach particularly with regards the procedures used for seeking consent.

Where the MHRA trial categorisation of risk (as outlined above) is available at the time of Research Ethics Committee (REC) review, committee members will be expected to take this into account when reviewing the proposed procedures for seeking consent, including the participant information sheet or other methods/media used for provision of information to potential participants²².

²¹ Brosteanu et al. Risk analysis and risk adapted on-site monitoring in non-commercial clinical trials. *Clinical Trials* 2009: 585-596

²² REC members may ask the applicant to state the risk category of a clinical trial of an IMP at the REC meeting. Where the risk category is available prior to submitting an application for ethical review then the risk category may be included as part of the covering letter for the application and/or within the protocol.

2.5. Applying a proportionate approach to pragmatic trials

Pragmatic trials²³ are a simple and cost effective way to address uncertainties about the relative merits of different treatments in common use. Such trials (also referred to as ‘simple trials’, ‘comparative effectiveness trials’, ‘non-Interventional trials’ or ‘low-intervention trials’²⁴) do not normally involve any extra interventions beyond those required as part of the patient’s routine care²⁵. They do not withhold effective treatment; rather they compare the effects of accepted or licensed interventions/therapies in the context of current clinical practice. Point of Care trials are a sub-group of pragmatic trials and usually embedded in routine practice. Patients are allocated to existing treatments and the data required for the research can often be collected through their electronic health records as such studies often take place in primary care.

As pragmatic trials involve relatively low risks and levels of burden which are no higher than that of standard medical care (e.g. category A trials) the methods used for seeking consent, including the amount of information provided up front and the time needed to consider participation, can be adapted in a proportionate manner so that they comply with the law but do not unduly burden either the patient or the care professional/researcher seeking consent.

Pragmatic trials involving non-drug interventions only need to comply with the “common law”, but research involving medicines taking place in the UK must also comply with The Medicines for Human Use (Clinical Trials) Regulations 2004 (referred to as ‘The Clinical Trials Regulations’) which set out in detail how patients should be recruited to such trials.

The Clinical Trials Regulations will apply where the drug that the patient receives **is decided by the research protocol, rather than by their doctor or other healthcare professional as part of clinical care**, *even if the trial only involves medicines that are licensed and are already in routine use*. The Medicines and Healthcare Regulatory Agency (MHRA) have produced an [algorithm \(PDF\)](#) which can help determine whether a trial is a CTIMP.

Participation in a CTIMP normally requires written consent²⁶. The Clinical Trials Regulations require that participants must have had the **nature, significance, implications and risks** of the trial explained to them in order for their consent to be valid. They must also have had an **interview with a member of the investigating team** where they are given the opportunity to discuss and better understand the objectives, risks and inconveniences of the trial and the conditions under which it is to be conducted.

In pragmatic trials these requirements may be achieved by the use of a short participant information sheet provided by the Investigator or GP/HCP (who, for the purposes of pragmatic trials, may also be considered to be a “member of the investigating team”). The PIS used in such low risk trials can be much shorter than the ‘traditional’ lengthy information sheets often used in more complex earlier phase drug trials.

²³ "Pragmatic trials measure effectiveness - the benefit the treatment produces in routine clinical practice. ...the design of a pragmatic trial reflects variations between patients that occur in real clinical practice and aims to inform choices between treatments. To ensure generalisability pragmatic trials should, so far as possible, represent the patients to whom the treatment will be applied". Roland M, Torgerson DJ. Understanding controlled trials. What are pragmatic trials? *BMJ* 1998;316:285.

²⁴ The forthcoming EU Clinical Trials Regulation (expected to come into effect by October 2018) introduces the term ‘low-intervention trial’ (a trial with minimal additional risk compared to normal clinical practice e.g. where the investigational medicinal product is covered by a marketing authorisation or, if that product is not used in accordance with the terms of the marketing authorisation, that use is evidence-based and supported by published scientific evidence on the safety and efficacy of that product)

²⁵ PRECIS-2 website: PRagmatic Explanatory Continuum Indicator Summary – is a clever acronym for a tool to help trialists designing clinical trials consider where they would like their trial to be on the pragmatic/explanatory continuum.

²⁶ The exception to this is emergency research where the participant may be unable to consent for themselves and a representative is not available.

It may be possible to set all of the necessary information out in a short participant information sheet ([see para. 2.5.2](#)), which, together with routine clinical information provided verbally by the HCP seeking consent about “the likely benefits, risks and burdens, including serious and common side effects”²⁷ and the detailed information contained in the Patient Information Leaflet (PIL) accompanying their prescription medicine(s), should normally provide sufficient information to enable a potential participant to make an informed decision regarding participation in a pragmatic trial at the time of the discussion regarding their clinical treatment. As the potential participant may simply be asked to take a standard treatment (licensed for their medical condition) and allow their anonymised medical data to be used for research, it may be reasonable to ask for their consent at the time of the clinical discussion with their HCP/member of the investigating team. However, patients should not feel under any pressure to take a decision in less time than they are comfortable with and any decision not to take part must always be respected.

If it is not possible to set all of the necessary information out in a single short participant information sheet, further supporting information²⁸ may be provided online (with the URL included in the short PIS) or as a separate paper document in line with a suggested ‘layered’ approach. However, the participant must be provided with an opportunity to access and consider all of the relevant information before they give their consent. For some pragmatic trials a decision will be required at the time of consultation (or very shortly after). In such cases, if the potential participant requires more time than is available to consider the available information then they should not be recruited to the trial.

2.5.1. A suggested proportionate procedure for seeking consent in a pragmatic trial

The use of the following proportionate procedure for seeking consent may be appropriate in the following circumstances:

- The study addresses a clinical question where there is uncertainty regarding the relative merits of relevant interventions
- The study involves little or no deviation from usual care (including monitoring for adverse effects, extra research-specific laboratory tests, questionnaires etc.)
- All treatment interventions (including “watch and wait” approaches to care) and medicines in the trial are used within the terms of their licence and/or are in routine use
- All other interventions/diagnostic tests are in routine use within the NHS and will be undertaken by those qualified to do so
- Research risks are no greater than those involved in standard care/not greater than minimal (e.g. extra blood tests/tissue samples taken during a ‘clinically directed’ procedure)
- The use of a proportionate approach to seeking informed consent does not adversely affect the rights or welfare of study participants
- Healthcare Professionals have the option of using an intervention other than the one assigned if they believe doing so is important for a particular patient²⁹

²⁷ General Medical Council. Good practice in prescribing and managing medicines and devices (2013)

²⁸ See HRA Consent and Participant Information Sheet Preparation Guidance: [Content: Participant Information Sheet - Supporting Information](#).

²⁹ Adapted from: Kim SY & Miller FG. Informed consent for pragmatic trials - the integrated consent model. *N Engl J Med*. 2014 Feb 20;370(8):769-72.; Faden et al. Informed consent, comparative effectiveness, and learning health care. *N Engl J Med*. 2014 Feb 20;370(8):766-8 and Weir et al. Veterans Healthcare Administration providers'

- The patient has not expressed a strong preference for any particular treatment.

If, during a clinical consultation the Healthcare Professional (HCP) decides that the patient would benefit from treatment where there is uncertainty amongst doctors regarding which drug for their condition is best and a pragmatic trial is taking place, the HCP may approach the patient to take part in that trial using an appropriate proportionate procedure such as:

1. HCP/GP verbally explains to patient that:

- *We have agreed that you would benefit from treatment. However, there is uncertainty amongst doctors regarding which licensed medicine/treatment is best.*
- *We would like to try and find out which one works best by asking you to take part in a research trial.*

2. The patient is given a Short Participant Information Sheet (see [para 2.5.2](#)) including information on how to access further information (if applicable).

3. Either the GP/HCP or (if the GP/HCP is not a member of the investigating team) a member of the investigating team asks the patient if they have any questions and discusses with them any matters they may wish to explore further (including routinely provided clinical information regarding the likely benefits, risks and burdens, including serious and common side effects of the allocated medicine).

4. If it has been possible to provide the patient with all of the relevant information at the outset³⁰:

- **If the patient agrees to participate their consent is documented in the electronic/paper records by HCP** (or other member of the investigating team)
- **Patient signs paper or electronic consent document during clinical consultation**
- **Patient receives allocated (standard) treatment and trial data collected from their medical records**

2.5.2. Example of a short Participant Information Sheet for use in pragmatic trials of licensed or commonly used medicines and treatments

Simple pragmatic trials involving participants taking routinely used, licensed medicines primarily for the purposes of their treatment will often be unblinded as there will no placebo arm and participants may receive a prescription rather than a blinded trial treatment. Consequently, detailed information related to the medicine itself (what the medicine is for, possible side effects, dosage, potential interactions etc.) will always be provided inside the

attitudes and perceptions regarding pragmatic trials embedded at the point of care. *Clin Trials* June 2014 11: 292-299, first published on March 20, 2014.

³⁰ Where this has not been possible or the potential participant requires more time than is available to consider the information then this may result in their not being eligible for recruitment to the trial.

standard pack and should also be given verbally by the HCP. This means that the additional information provided to the patient about the *research* component (randomisation, data collection and use, additional risks etc.) can be relatively brief.

This also applies to pragmatic trials involving ‘unlicensed medicines’³¹ i.e. medicines that are used outside the terms of their UK licence or which have no licence for use in the UK but are commonly used in some areas of medicine, particularly paediatrics, psychiatry and palliative care due to the absence of suitable licensed treatments.

Where the outcome data can be extracted anonymously via electronic records or via the patient’s HCP, the consent process can be focussed on the research intervention itself. However, in other studies, where it is not possible to extract outcome data in an anonymised way, informed consent will also need to be sought for accessing and sharing the patient’s identifiable data and/or samples in addition to the intervention.

The following is an example of a short Participant Information Sheet that may be adapted and used in a pragmatic trial conducted to compare two medicines or other treatments that are routinely prescribed within the NHS.

[N.B. Whilst the example here is presented in a traditional text format, it may be incorporated into a more user-friendly multimedia format. This PIS may also be adapted for use in other low-risk studies.]

We are inviting you to take part in a research project called [Trial name].

You do not have to take part if you do not want to.

Please read this information which will help you decide.

Research Title: [e.g. *A research study to find out if [X] is better than [Y] for treating people with [medical condition]*].

IRAS Reference Number:

EudraCT No./EU trial number³²/Other registry No. [As applicable]

Why am I being asked to take part in this research?

You and your doctor have agreed that you would benefit from treatment for [patient’s medical condition].

[X] and [Y] are [two] licensed/commonly used treatments routinely used to treat [patient’s medical condition] and they are believed to be equally good. However, we do not know which is best.

In order to find out whether [X] or [Y] is better we are inviting patients like you to take part in a research project in which some patients will be given [X] and some patients [Y] and the two groups of patients compared.

Although you would not receive any extra benefit from taking part, research like this helps to continually improve the treatments and care provided to all patients now and in the future.

Do I have to take part?

No.

³¹ See the General Medical Council’s ‘Good practice in prescribing and managing medicines and devices (2013)’ - Prescribing unlicensed medicines: http://www.gmc-uk.org/guidance/ethical_guidance/14327.asp for further information

³² Required by forthcoming [EU Clinical Trials Regulation](#)

It is entirely up to you to decide. If you do not want to take part that's OK. Your decision will not affect the quality of care you receive.

If you decide NOT to take part you and your [GP/Doctor/healthcare professional] will agree on which treatment you will receive. This may be the same as the treatment you would have received by taking part in this research project.

If you do decide to take part you are free to withdraw at any time, without giving a reason, by contacting your [GP practice/Doctor/healthcare professional].

What will I need to do if I take part?

If you agree to take part in this research you will be given *either* [X] or [Y] both of which are used to treat [patient's medical condition].

[Or if cluster design³³: If you agree to take part in this research you will be given [X/Y] which is routinely used to treat [patient's medical condition] in the NHS but may not be the treatment usually prescribed by [your GP/GP practice/Doctor/this hospital etc.].

Everybody taking part in this study, in this [describe cluster unit: ward/hospital/GP practice etc.] will be treated with [X].]

You do not need to do anything more. All the information needed for the research (but not anything that could identify you) will be collected from your medical records and shared with the researchers.

[Describe any additional samples/tests etc. beyond normal care]

If you choose to take part in this study, it will last for [duration of individual participant's involvement]. The entire research will last for [duration of study]. You will not have to make any extra visits to your doctor over and above those needed for your normal care.

At the end of the research, or earlier if you experience any unpleasant side effects, your [GP/Doctor/healthcare professional] will discuss with you whether you should continue with the treatment you are taking or switch to another treatment.

What are the disadvantages/risks?

[There are no extra risks involved in taking part in this research.]

[There are only minimal risks involved in this research. These are (provide detail of any potential risks due to additional research procedures)]

The possible side-effects of the medicine you are given will be explained by your [GP/Doctor/healthcare professional] and are also provided in the information leaflet that comes with that medicine.

If we do find that one treatment is better than the other for you the trial will be stopped *[and you will be switched to the better treatment]*

A summary of the results of this research will be made available to all those taking part who would like to receive this³⁴. *[Provide details of how the results will be made available]*

What will happen to information collected about me during the study?

³³ A type of research design that randomises the drugs or treatments being investigated to different groups or clusters of individuals (such as households, primary care practices, hospital wards, classrooms, neighbourhoods or communities), rather than individuals.

³⁴ See HRA "Information for participants at the end of a study: Guidance for Researchers" for more information: <http://www.hra.nhs.uk/documents/2014/09/information-participants-end-study-guidance-researchers.pdf>

Your medical information will be kept strictly confidential by your doctor. The researchers will only be given as much information from your medical records as is needed for this research and that information will be anonymised. They will not be given your name, where you live or anything that could identify you.

Who is organising and funding the research?

This study is being carried out by [details of researcher(s), Sponsor and institution(s)].

[If applicable: The researchers will pay your GP/GP practice/Hospital etc. £[amount] for including you in this study.]

The research is funded by [name of funder (if different from Sponsor)].

Thank you for reading this information and for considering taking part in this research

Further Information: You can ask your [GP/Doctor/healthcare professional or other nominated person] any questions you may have about the study.

You may also obtain more detailed information about this research, including how your medical information will be used, your privacy protected, and the compensation arrangements in the unlikely event that anything goes wrong from [this website: [URL] and/or your GP/Doctor/healthcare professional etc.]

Contact Details:

Your [GP/Doctor/healthcare professional]:

Chief Investigator:

PIS Version No. Date.....

2.6. Consent in postal/self-completion surveys

For postal/online surveys or self-administered questionnaire-based research, it is not necessary to include a separate Participant Information Sheet or consent form. Participants should still be provided with sufficient information to enable them to reach an informed decision whether to complete and return the survey/questionnaire or not but this may be included as a short introductory paragraph as part of the survey/questionnaire itself or included in a short covering letter.

Provided that the information adequately describes in broad terms the nature and purpose of the research, why they are being invited to take part, how the information collected will be used and stored, and how the findings might be made available to them, then completion and return of the survey/questionnaire will indicate consent on behalf of the participant.

Where the research involves sensitive questions and/or potentially greater threats to participant confidentiality then this should be clearly spelt out in the covering letter to participants; there is still no need to seek separate written consent to take part in a postal survey prior to the participant completing the questionnaire.

2.7. Good Clinical Practice (GCP) training for those seeking consent: A proportionate approach

Good Clinical Practice (GCP) is an international ethical and scientific quality standard for designing, conducting, recording and reporting clinical trials that involve the participation of human subjects³⁵.

The International Conference on Harmonisation GCP Guideline (ICH GCP) (as adopted by the Committee for Medicinal Products for Human Use (CHMP)) is part of European guidance, as an element of EudraLex Volume 10, and as such should be taken into consideration, where appropriate, as an established standard for GCP. In particular, if a study is to be included as part of a marketing authorisation application then it is an expectation that ICH GCP should be complied with, and this is referred to in the annexes to the Notice to Applicants (Volume 2B) for the Common Technical Document.

Both the HRA and the MHRA advocate a proportionate approach to the application of GCP to the conduct of clinical trials and the appropriate training of staff involved, including those seeking consent from potential participants.

Sponsors of CTIMPs which are **not** to be included as part of a marketing authorisation application can choose to comply with ICH GCP as a standard in its entirety or they can take a more proportionate approach depending on the nature of the trial. Further information about this can be found in the MHRA guidance on risk adapted approaches in the management of CTIMPs.³⁶

However, it is important to emphasise that for **all CTIMPs** it is the “**conditions and principles**” of GCP set out in the The UK Clinical Trials Regulations (SI 2004/1031, as amended) (see [Annex A](#)) that *must* be complied with. The *principles* of GCP are high level and may be interpreted in relation to the individual trial and *in proportion to the risks posed to the participants and to the integrity of the results*.

The UK Clinical Trials Regulations stipulate that:

“each individual involved in conducting a trial shall be qualified by education, training and experience to perform his tasks” (Schedule 1, Part 2, 2).

Staff involved in the conduct of clinical trials need to be appropriately trained so that all investigators know what is expected of them in relation to trial procedures, and in order to ensure that the conditions and principles of GCP can be applied to any trial in a proportionate manner.

The training required does not need to follow a generic syllabus, format or prescribed timing but should be appropriate and proportionate to the activities undertaken by staff involved in the clinical trial. It should be tailored to the specific roles and responsibilities being undertaken by an individual. For example, it may be appropriate that some staff only receive an overview of the clinical trial, which could be in the form of a written summary; or they could simply be made aware of the local trial team contacts and have an awareness of, rather than a detailed knowledge of, ICH GCP requirements.

In the case of pragmatic trials, involving only minimal risk related to the research, it may be appropriate for the HCP to simply have an awareness of GCP requirements (which could be

³⁵ ICH Harmonised Tripartite Guideline - Guideline For Good Clinical Practice E6(R1) Current Step 4 Version Dated 10 June 1996

³⁶ MHRA- Risk-adapted Approaches to the Management of Clinical Trials of Investigational Medicinal Products, Oct 2011.

achieved by self-directed learning/provision of written learning materials etc.). For example, a practice nurse taking a blood sample in a pragmatic trial for the purposes of research, might be considered to be undertaking an activity that the HCP is suitably qualified to undertake by virtue of their education, training and experience without undertaking detailed GCP training.

Training/awareness in the aspects of GCP relevant to that role would be considered acceptable (for example, recording of adverse events, documentation of activities in source notes or case report form (CRF), escalating any issues they identify as appropriate).

For certain trials it may be necessary for staff involved in trial activities to be aware of other regulatory requirements outside those of GCP. For example, healthcare professionals retaining tissue samples should be aware of the Human Tissue Act.

It should be noted that there is no legal requirement for other types of research (i.e. studies which are not clinical trials) to be conducted in accordance with the conditions and principles of GCP. However, it is still important that such research is always conducted in a manner that provides public assurance that the rights, safety and wellbeing of research participants are protected and that research data are reliable. Members of the research team in such studies are expected to be qualified by education, training or experience but should not be required or expected to undertake GCP training.

The HRA has previously issued the following general [statement](#)³⁷ regarding GCP training:

- For research, training should be appropriate and proportionate to the type of research undertaken, and should cover the responsibilities of researchers set out in relevant legislation and standards.
- There is no set requirement for the frequency of such training. Researchers are expected to maintain awareness of current standards through reference to published guidance and relevant policies.
- Training should be updated when legislation has changed, new policies or practice have been implemented, different research activities are to be undertaken, or a significant period of time has elapsed since research activities have been conducted.
- For research involving CTIMPs, there is a requirement for GCP training. However, the timing of this training is not specified in legislation or guidance but should be appropriate and proportionate

The MHRA also issued a statement in June 2012 to clarify the requirements for GCP training. The statement is on their website at [‘What is the MHRA’s position on Good Clinical Practice \(GCP\) training?’](#) and is summarised below:

- The UK Clinical Trials Regulations (SI 2004/1031, as amended) state that no person shall conduct a clinical trial otherwise than in accordance with the conditions and principles of GCP (Regulation 28) and that each individual involved in conducting a trial shall be qualified by education, training and experience to perform his tasks (Schedule 1, Part 2, 2).
- The frequency of GCP training is not defined in the regulations. How often this training is repeated is a business decision for the organisation concerned.

³⁷ Training requirements for researchers – progress update (v1.5 2012-07-27)

- Training needs may range from a detailed knowledge of GCP principles and associated UK Regulations and European guidance to an awareness of particular GCP principles, and training can be tailored accordingly.
- If an activity is part of a person's normal clinical role and all other protocol activities are undertaken by a member of the research team, then no GCP training may be required; however this should be reviewed as part of the risk assessment for a trial.
- The MHRA strongly recommends training in relevant aspects of GCP for anyone involved in conducting CTIMPs, even if the activities are part of an individual's routine job. - GCP training can be provided in a range of formats, including face-to-face, web-based and as self-directed reading.
- On inspection, MHRA GCP inspectors will look for evidence that individuals involved in the conduct of CTIMPs have received adequate training in GCP and appropriate legislative requirements commensurate with their roles and responsibilities.

Organisations involved in the conduct of CTIMPs are recommended to read the [full MHRA statement](#) and review their policies and procedures in light of this statement.

Annex A

The Medicines for Human Use (Clinical Trials) Regulations (2004) [as amended³⁸]

CONDITIONS AND PRINCIPLES WHICH APPLY TO ALL CLINICAL TRIALS

Principles based on Articles 2 to 5 of the GCP Directive³⁹

1. The rights, safety and well-being of the trial subjects shall prevail over the interests of science and society.
2. Each individual involved in conducting a trial shall be qualified by education, training and experience to perform his tasks.
3. Clinical trials shall be scientifically sound and guided by ethical principles in all their aspects.
4. The necessary procedures to secure the quality of every aspect of the trial shall be complied with.
5. The available non-clinical and clinical information on an investigational medicinal product shall be adequate to support the proposed clinical trial.
6. Clinical trials shall be conducted in accordance with the principles of the Declaration of Helsinki.
7. The protocol shall provide for the definition of inclusion and exclusion of subjects participating in a clinical trial, monitoring and publication policy.
8. The investigator and sponsor shall consider all relevant guidance with respect to commencing and conducting a clinical trial.
9. All clinical information shall be recorded, handled and stored in such a way that it can be accurately reported, interpreted and verified, while the confidentiality of records of the trial subjects remains protected.

Conditions based on Article 3 of the Directive

10. Before the trial is initiated, foreseeable risks and inconveniences have been weighed against the anticipated benefit for the individual trial subject and other present and future patients. A trial should be initiated and continued only if the anticipated benefits justify the risks.
11. The medical care given to, and medical decisions made on behalf of, subjects shall always be the responsibility of an appropriately qualified doctor or, when appropriate, of a qualified dentist.
12. A trial shall be initiated only if an ethics committee and the licensing authority comes to the conclusion that the anticipated therapeutic and public health benefits justify the risks and may be continued only if compliance with this requirement is permanently monitored.

³⁸ The conditions and principles which apply to all clinical trials were amended by The Medicines for Human Use (Clinical Trials) Amendment Regulations 2006 (S.I. 2006 No. 1928)

³⁹ Commission Directive 2005/28/EC

13. The rights of each subject to physical and mental integrity, to privacy and to the protection of the data concerning him in accordance with the Data Protection Act 1998 are safeguarded.

14. Provision has been made for insurance or indemnity to cover the liability of the investigator and sponsor which may arise in relation to the clinical trial.