

Seeking informed consent for simple and efficient trials in the NHS

Draft guidance: For comment



Contents

1. Introduction
2. Draft guidance/example short information sheet
3. Consent scenarios
4. Relevant legal, governance and ethical frameworks

Annexes:

1. Articles 29 and 30 of the EU Regulation on Clinical Trials
2. Article 59(1) of Directive 2001/83/EC on the Community code relating to medicinal products for human use.

1. Introduction

1.1. The Health Research Authority (HRA)

The HRA was established in December 2011 in England 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. The purpose of this call for comment on draft guidance

The purpose of this document is to seek comments on proposed HRA guidance on **simpler procedures for seeking consent from patients to take part in large-scale simple and efficient research trials** within the NHS.

Your comments will inform the development of this HRA guidance representing an agreed ethical framework for seeking consent in such trials that is proportionate to the low risks involved.

The deadline for comments is 28 November 2014. Comments should be sent using the response form provided with this document (See section 5. 'How to Respond')

Why is it important to conduct such trials?

In many cases we don't always know (due to a lack of evidence) which of the large number of treatments routinely used in the NHS is best for an individual patient, or group of patients. It's important, therefore, to compare the medicines and other treatments used in order to better inform evidence-based treatment¹.

The best way to get the evidence is to carry out large scale research with the help of patients who are willing to agree to take part so that we can reliably compare the different treatments available. This can be costly and time-consuming.

However, such trials could be carried out more **simply and efficiently by recruiting patients into the research at the time they are prescribed their medicine or treatment at the GP Surgery or hospital.**

These trials often referred to as "pragmatic trials"², are cheaper to run than large-scale drug trials and present little or no risk to the participant as they would receive a standard treatment routinely prescribed within the NHS for their condition. In many cases this will be exactly the same treatment they would receive if they declined to take part in the research. The patients recruited to these trials can be followed up through their electronic health records held by their GP or, where applicable, their hospital medical records. **For the vast**

¹ In line with the Secretary of State for Health's statutory duty to promote "(a) research on matters relevant to the health service, and (b) the use in the health service of evidence obtained from research". Health and Social Care Act 2012.

² "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.

majority of these types of trials the patient would not be asked to do anything other than agree to be randomised (rather like tossing a coin or rolling a die) **to a standard treatment and to the use of their data for purposes of the research.** For some trials it might also be necessary to ask them to agree to some additional research procedures such as extra blood tests or answering a simple questionnaire.

These 'simple and efficient trials' can be randomised in two ways:

- Individual randomisation where each patient who is suitable to join the trial will be individually allocated to an intervention, or
- Cluster randomisation where separate GP practices, wards, or hospitals are randomised to provide different interventions.

This latter type of trial is called a **cluster randomised trial³** or '**cluster trial**' for short.

A forthcoming piece of European legislation (the 'Clinical Trials Regulation' likely to come into force in 2016/17) will allow informed consent to be obtained in cluster trials involving drugs by what it refers to as '*simplified means*'. Whilst this EU Regulation is not yet applicable to drug trials we need to consider what the practical and ethical implications of this important provision are now so that that we are able to provide appropriate guidance regarding the seeking of consent by simplified means once this Regulation is in force.

Why do we need guidance on seeking consent for such trials?

'Simple and efficient' trials could involve routine interventions ranging from testing hospital mattresses to comparing licensed medicines. Whilst trials involving mattresses or other non-drug interventions only need to comply with what is known as the "common law"⁴, research involving medicines also needs to comply with complex legal regulations (known as The Clinical Trials Regulations) setting out in detail how patients should be recruited to such trials in the U.K. (see para 4.2. 'UK Legal Framework' for more information). In order to comply with these regulations patients recruited to them must have had the nature, significance, implications and risks of the trial explained to them in a 'prior interview' with a member of the investigating team. These Regulations apply to all drug trials, where the drug the patient receives is decided by the research protocol rather than their doctor, regardless of whether they are looking at a completely new experimental medicine or comparing medicines that have been shown to be safe and are already in routine use.

We believe guidance is needed in order to facilitate simple and efficient trials looking at the effectiveness of routinely used standard treatments so that patients can be recruited in a way that complies with the law but does not overly burden either the patient or the health care professional seeking consent. Central to this more proportionate approach is the use of a suggested short information sheet template (see para 2.7).

1.3. Simple and efficient trials: A real example

Simple, pragmatic trials are already taking place within the NHS. Here is an example of one such study involving statins which investigated the feasibility of conducting such trials. Statins are routinely prescribed drugs which help to lower the level of low-density lipoprotein (LDL) cholesterol (often referred to as "bad cholesterol") in the blood:

³ 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.

⁴ law developed by judges through decisions of courts and similar tribunals, as opposed to statutes adopted through the legislative process or regulations

RETRO-PRO: The effectiveness of simvastatin compared to atorvastatin: an e-clinical randomised trial within a research database in routine clinical practice - a feasibility study. (ISRCTN33113202⁵) (REC Reference: 10/H1102/30⁶)

Summary

This study aimed to find out whether it is possible and useful for the NHS to use electronic health records (EHRs) held by GPs to carry out the research that is usually done in randomised trials.

Many patients are prescribed statins or lipid-lowering drugs for heart disease. Although there are laboratory data suggesting that some types of statins may be better than others, there is not much evidence for doctors to decide what type of statin is best.

This study collected information on what happens to 300 patients after starting statin treatment using information routinely collected in the NHS.

Potential participants were identified through the GP medical record software system and, at their next GP visit, asked if they would participate in the research study.

A study information sheet and consent form were printed from the software system and given to the patient to read. Patients were able to discuss the study with their GP and if they were happy to take part signed the printed consent form.

Patients were informed that both statins were widely prescribed and that it was hoped that this trial would help decide whether the "simple study methodology" of recruitment in routine clinical care and data collection using standard NHS records could be used to run large-scale studies in general practice. It also made clear that they could withdraw from the research by not redeeming the prescription for the study drug and that they could return to their GP for a further consultation, in which case their GP may still prescribe them the same statin.

Consenting patients were provided with a statin prescription (at the same visit as the recruitment) and their data collected for 3 months. They were also asked to provide two blood samples.

The information used in this study was fully anonymised (the researchers did not know the patient's name and contact details) and was collected from the General Practice Research Database (widely used for the monitoring of side-effects and observational research).

Conclusions

“EHR point-of-care trials are feasible, although the recruitment of clinicians is a major challenge owing to the complexity of trial approvals. These trials will provide substantial evidence on clinical effectiveness only if trial interventions and participating clinicians and patients are typical of usual clinical care and trials are simple to initiate and conduct. Recommendations for research include the development of evidence and implementation of risk proportionality in trial governance and conduct.”⁷

⁵ <http://www.controlled-trials.com/ISRCTN33113202>

⁶ <http://www.nres.nhs.uk/researchsummaries/?entryid29=174456&q=0%7eISRCTN33113202%7e>

⁷ van Staa TP, Dyson L, McCann G, Padmanabhan S, Belatri R, Goldacre B, et al. The opportunities and challenges of pragmatic point-of-care randomised trials using routinely collected electronic records: evaluations of two exemplar trials. Health Technol Assess 2014;18(43) <http://www.journalslibrary.nihr.ac.uk/hta/volume-18/issue-43>

2. Draft guidance, consent scenarios and draft patient information sheet

2.1. The Importance of informed consent

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

The requirement to seek informed consent directly from research participants should only be set aside in exceptional, well defined circumstances provided for in law (e.g. research involving individuals unable to provide consent for themselves).

For consent to be considered both legal and ethical it must be:

- Given by a person with capacity;
- Voluntarily given, with no undue influence;
- Given by someone who has been adequately informed;
- A fair choice⁸.

2.2. Requirement for a written information sheet

It should be noted that it is not a legal requirement for information about any trial to be provided in the form of a written information sheet, in some circumstances it could be given verbally. However, providing the patient with a written information sheet potentially shortens the consent 'interview' and allows them to refer back to the information at a later date.

Unless there are good reasons for not doing so, a permanent and portable copy (paper, audio, CD/DVD, braille etc.) of the information sheet should normally be made available to all potential research participants.

2.3. Requirement for a written consent form

The function of a consent form is to record the participant's decision, indicate that the process was conducted appropriately and that a suitable discussion occurred. A signature on a consent form does not in itself make consent legally valid.

For Clinical Trials of Investigational Medicinal Products (CTIMPs) the participant's consent must be documented in writing.

For other types of research, consent can be written but it can also be oral or non-verbal (i.e. a signed consent form is not always required provided that the consent itself is appropriately documented and the record available for inspection).

However, where consent is required it should normally be documented and available for inspection no matter what type of research is being undertaken unless there are good reasons for not doing so and this has been agreed with the REC.

2.4. Proportionality and simplified consent procedures

⁸ HRA Consent and Participant Information Sheet - Preparation Guidance (<http://www.hra-decisiontools.org.uk/consent/principles-general.html>)

In all research the procedures used to obtain consent, including the information provided, should always be *proportionate* to the nature of what is proposed, the risk of the research and the ethical issues at stake. The amount of information that needs to be given to a potential research participant, in order for them to make up their mind about taking part, will vary depending upon the complexity and burden of the proposed research:

The more research deviates from established clinical practice the greater the amount of information that needs to be provided to potential participants.

Complex research studies involving a significant number of interventions and burden for participants will require more detailed information to be provided about the nature of the research than simple research studies involving little or no additional burden (beyond those related to their clinical treatment).

This guidance explores the circumstances in which simplified procedures for seeking consent (including the level of information required) may be used in cases where the research imposes little or no burden and little or no risk to the participants.

For example, in simple and efficient drug trials conducted in a primary care setting the burden imposed by the legal requirement for a 'prior interview' with the investigator, or another member of the investigating team could be reduced by the use of a short information sheet provided by the GP/Investigator (we suggest that in this context the GP may be considered a member of the investigating team). If, during the clinical consultation the GP decides that the patient would benefit from treatment where there is uncertainty amongst doctors regarding which licensed drug for their condition is best and a simple and efficient trial is taking place, then the GP could approach the patient to take part in that trial.

The GP would verbally explain that due to uncertainty regarding which available drug works best research is being conducted to find out. They provide the patient with a short information sheet, ask if the patient has any questions and seek their consent to be part of the trial. The patient/participant would receive the allocated (standard) treatment and their data would be collected from their medical records. No further involvement would be required.

In para 2.7 below we provide a possible example of a short information sheet that might be used in the above scenario. Detailed information regarding the drug and its possible side effects would not need to be added to the information sheet as this would be contained in the Patient Information Leaflet (PIL) accompanying their drug prescription.

2.5. Suggested general principles regarding the seeking of informed consent:

- **Informed consent is central to the ethical conduct of research and should be sought in all cases unless a strong justification can be provided for dispensing with this important requirement**
- **Informed consent procedures should always be proportionate to the nature of what is proposed, the risk of the research and the ethical issues at stake**
- **Informed consent should always be documented⁹**

⁹ "Consent does have to be indicated in some way: for many studies, consent can be written, oral or non-verbal. However, in Clinical Trials of Investigational Medicinal Products (CTIMPs) consent is not considered legal unless it is in writing. The function of a consent form is to record the participant's decision, and to indicate that the process was conducted appropriately and with suitable discussion. A signature on a consent form does not in itself make consent valid." HRA Consent and Participant Information Sheet - Preparation Guidance (<http://www.hra-decisiontools.org.uk/consent/principles-general.html>)

2.6. Suggested specific principles regarding seeking consent in simple and efficient trials:

The HRA suggest that simplified consent procedures may be used in line with the following principles:

- Following the normal consent process would place a disproportionate burden in terms of time and resources in relation to the perceived risk
- The study addresses a clinical question where there is uncertainty regarding the relative merits of relevant interventions
- All medicines used in the trial are in routine use and within the terms of their licence
- The study involves little or no deviation from usual care (including monitoring for adverse effects, extra research-specific laboratory tests, study visits, questionnaires etc.)
- All 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 simplified means to obtain consent does not adversely affect the rights or welfare of study participants
- Healthcare Professionals (HCPs) have the option of using an intervention other than the one assigned if they believe doing so is important for a particular patient¹⁰
- Patient has not expressed a strong preference for any particular treatment

2.7. Suggested short information sheet for use in simple and efficient trials

The following is an example of a short participant information sheet (PIS) that could be used in a simple trial conducted to compare two licensed medicines that are routinely prescribed within the NHS.

In the case of simple and efficient trials involving participants taking routinely used licensed medicines (primarily for the purposes of their treatment), detailed information related to the medicine itself (what the medicine is for, possible side effects, dosage, etc.) will always be provided inside the standard pack (see Annex 2 for a full list of the information provided). This means that the information provided to the patient about the *research* component (randomisation, data collection and use etc.) can be relatively brief.

¹⁰ 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' attitudes and perceptions regarding pragmatic trials embedded at the point of care. Clin Trials. 2014 Mar 20;11(3):292-299. [Epub ahead of print]

**We would like to invite you to take part in a research project.
You do not have to take part if you do not want to.**

Please read this information leaflet to help you decide.

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

**REC Reference Number:
EudraCT No./ EU trial number¹¹**

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] treatments licensed to treat *[patient's medical condition]* and they are believed to be equally good. However, we do not know this for certain.

In order to find out whether [X] or [Y] is better for patients with your medical condition 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.

If you decide to take part you will receive either [X] or [Y] as your treatment.

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.

It is entirely up to you to decide. If you would prefer not to take part that's OK. Your decision will not affect the standard of NHS care you receive.

If you decide NOT to take part you and your GP will agree on which treatment you will receive. This may be the same as the one 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.

What will happen to me 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 in the NHS to treat *[patient's medical condition]*.

The actual treatment YOU get will be decided at random (like tossing a coin to make a decision) and NOT by your doctor.

You do not need to do anything more. If you agree to take part 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]

You will be one of [number of patients to be recruited] patients taking part in this research which will last for [duration of study]. At the end of the research, or earlier if you experience any unpleasant side effects, your GP will discuss with you whether you should continue with the treatment given to you or switch to another treatment.

¹¹ Required by forthcoming EU Clinical Trials Regulation

What are the risks?

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

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

The possible side effects of the medicine you will take are included 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 given the better treatment, if suitable, and you are not already taking it.]

A summary of the results of this research will be sent to all participants who would like to receive this.

Will my taking part in this study be kept confidential?

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. 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) and institution(s)]. [*If applicable*: The researchers will pay your GP £[amount] for including you in this study.] The research is funded by [funder]

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

Further information: You can ask your GP any further questions you may have about the study.

You may also obtain further 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 the following website: [insert URL]

Contact details:

Your G.P.:
Chief Investigator:

PIS Version No. Date.....

The Health Research Authority currently also provides online guidance (<http://www.hra-decisiontools.org.uk/consent/principles-general.html>) on how to prepare participant information sheets and other documents to support the seeking of consent. This includes information on:

- The principles of consent (both ethical and legal)
- How the principles relate to preparation and use of a participant information sheet (PIS) and consent form
- Recommended content of a PIS and consent form; and
- Design and style of an effective PIS and consent form

The online guidance should be considered as a framework, not a rigid template. Investigators should always think carefully about how best to inform potential participants.

One size does not fit all: you do not need to produce the same information sheet and consent form to support consent for a questionnaire study as you would to recruit into a complex drug trial.

The best way to make sure that any information given to potential participants is fit for purpose is to test it with patient groups and/or other members of the public.

3. Consent scenarios

The following scenarios set out four separate contexts in which simple and efficient trials might take place along with suggested options for seeking consent from patients in a way that is proportionate to the low level of risk involved.

(Please note we are not seeking comments on whether these scenarios accurately reflect clinical practice nor the legal, practical or logistic issues of implementing such trials but on the acceptability of the procedures proposed.)

Scenario 1	
Explicit consent (short information sheet)	
Clinical trial of Statins (GP Surgery)	
Scenario:	Comparison of licenced statins to reduce low-density lipoprotein (LDL) cholesterol - Individual Patient Randomisation
NHS context:	Primary Care (General Practice)
Key factors:	<ul style="list-style-type: none"> • The drug that the patient would receive is decided by the research protocol (randomised) and not the GP • This is a Clinical Trial of Investigational Medicinal Products (CTIMP) • All trial drugs are licenced and in routine use in the NHS • There is insufficient evidence regarding comparative effectiveness • Systematic reviews have been conducted and genuine uncertainty exists regarding which medicine is best • Participants will know what drug they have been given – Relevant medicine ‘patient information leaflets’ (PIL) are available and provided to patients with their medicine as normal. • Only routine clinical data will be collected • Patients are not subjected to any risk greater than those related to standard care • The study involves little or no deviation from usual care (including monitoring for adverse effects, extra research-specific laboratory tests, study visits, questionnaires etc.)

Possible consent option:	<p>Explicit consent sought by GP/Other Health Care Professional (HCP)</p> <p>HCP verbally explains to patient that:</p> <ul style="list-style-type: none"> - <i>We have agreed that you would benefit from a treatment with a statin. However, there is uncertainty amongst doctors regarding which licensed statin is best.</i> - <i>We wish to find out which one works best by asking you to take part in a research trial.</i> • HCP gives patient short Participant Information Sheet (see para 2.7) including link to further online information. • HCP asks the patient if they have any questions. • If patient agrees, on basis of verbal explanation/PIS, their consent documented in patient electronic records by HCP (GP/Practice Nurse/Pharmacist) • Patient signs paper consent document
---------------------------------	--

Scenario 2

‘Deemed’ consent (opt-out) - Patient asked to confirm consent

Randomised Cluster Trial (GP Surgery)

Scenario:	Comparison of licenced statins to reduce low-density lipoprotein (LDL) cholesterol - Cluster trial – Randomisation at GP Clinic level
NHS context:	Primary Care (General Practice)
Key factors:	<ul style="list-style-type: none"> • The GP practice is the unit of randomisation i.e. whilst different GP surgeries will prescribe different drugs in the trial all eligible patients within a single GP surgery will be given the same drug • This is a Clinical Trial of Investigational Medicinal Products (CTIMP) • All trial drugs are licenced and in routine use in the NHS • There is insufficient evidence regarding comparative effectiveness • Systematic reviews have been conducted and genuine uncertainty exists regarding which medicine is best

	<ul style="list-style-type: none"> • Participants will know what drug they have been given – Relevant medicine ‘patient information leaflets’ (PIL) are available and provided to patients with their medicine as normal. • Only routine clinical data will be collected • Patients are not subjected to any risk greater than those related to standard care • The study involves little or no deviation from usual care (including monitoring for adverse effects, extra research-specific laboratory tests, study visits, questionnaires etc.)
Possible consent option:	<p>Implicit/Deemed consent (opt-out) - Confirmed</p> <ul style="list-style-type: none"> - Poster on prominent display in GP surgery waiting room explaining that a trial of statins is taking place. The poster contains information equivalent to the information provided in the example short Participant Information Sheet (see para 2.7). This includes a web address for further online information. Translated versions of the poster used as necessary. - Paper copies of the information sheet are available on request. - Poster includes explanation that all patients will be included in the trial if they need to be prescribed a statin and meet the inclusion criteria UNLESS they explicitly inform the GP or other surgery staff that they do not wish to take part (i.e. Opt-Out). • During consultation with patient HCP reiterates that unless the patient disagrees (opts-out) they will be included in a clinical trial and their treatment determined at random between existing routine treatments. HCP explains where further information can be obtained (e.g. short information sheet/website).

Scenario 3

‘Deemed’ consent (opt-out) – Patient not asked to confirm consent

Randomised Cluster Trial (GP Surgery)

Scenario:	Comparison of licenced statins to reduce low-density lipoprotein (LDL) cholesterol - Cluster trial – Randomisation at GP Clinic level
NHS context:	Primary Care (General Practice)
Key factors:	

	<ul style="list-style-type: none"> • The GP practice is the unit of randomisation i.e. whilst different GP surgeries will prescribe different drugs in the trial all eligible patients within a single GP surgery will be given the same drug • This is a Clinical Trial of Investigational Medicinal Products (CTIMP) • All trial drugs are licenced and in routine use in the NHS • There is insufficient evidence regarding comparative effectiveness • Systematic reviews have been conducted and genuine uncertainty exists regarding which medicine is best • Participants will know what drug they have been given – Relevant medicine ‘patient information leaflets’ (PIL) are available and provided to patients with their medicine as normal. • Only routine clinical data will be collected • Patients are not subjected to any risk greater than those related to standard care • The study involves little or no deviation from usual care (including monitoring for adverse effects, extra research-specific laboratory tests, study visits, questionnaires etc.)
<p>Possible consent option:</p>	<p>Implicit/deemed consent (opt-out) – Not confirmed</p> <ul style="list-style-type: none"> - Poster on prominent display in GP surgery waiting room explaining that a trial of statins is taking place. The poster contains information equivalent to the information provided in the example short Participant Information Sheet (see para 2.7). This includes a web address for further online information. Translated versions of the poster used as necessary. - Paper copies of the information sheet are available on request. - Poster includes explanation that all patients will be included in the trial if they need to be prescribed a statin and meet the inclusion criteria UNLESS they explicitly inform the GP or other surgery staff that they do not wish to take part (i.e. Opt-Out). • HCP enrolls patient if they meet the inclusion criteria but DOES NOT provide any further information (either written or verbal) regarding research component nor seek explicit consent from the patient. • HCP documents patient enrolment into trial along with all refusals and withdrawals. <p>(NB this option would not be legal under the current Clinical Trials Regulations but might be permitted by the forthcoming EU Clinical Trial Regulation – see para 3.6)</p>

Scenario 4

No consent for research intervention

Cluster trial (Hospital Ward)

Scenario:	Pressure relieving mattresses trial - Cluster Randomisation at hospital ward level
NHS context:	Secondary Care
Key factors:	<ul style="list-style-type: none">• Non-drug trial – compliance with common law only• Trial mattresses are both in routine use• There is insufficient evidence regarding comparative effectiveness• Systematic reviews have been conducted and genuine uncertainty exists regarding which mattress is best• Only routine clinical data will be collected• Patients are not subjected to any risk greater than those related to standard care• No additional intervention following randomisation• No interventions other than standard care
Possible consent option:	<p>No consent sought for the research intervention as both mattresses represent standard care and it would be impractical to move the patient to a different ward if the trial mattress is not what they would prefer</p> <p>Explicit verbal consent is sought for access to their medical records for the purposes of the research and documented in the patient's notes.</p>

4. Relevant legal, governance and ethical frameworks

Clinical research in the UK takes place within a complex landscape of legal requirements, research governance policy and ethical guidance, all of which determine the limits to acceptable procedures for seeking and obtaining consent. This section sets out the background regarding important frameworks that impact upon how information regarding research needs to be provided and how consent needs to be documented.

4.1. Key points

Drug trials:

- **What information must be provided?** Information on the nature, significance, implications and risks of the trial
- **How must it be provided?** By prior interview with the investigator or a member of the investigating team (other means, such as information sheets, may be used in addition).
- **How must consent be recorded?** In writing. Dated and signed, or otherwise marked' by the participant

Non-Drug Trials:

- **What information must be provided?** Information on the broad nature and purpose of the research, material/significant risks and benefits and alternatives
- **How must it be provided?** Not specified
- **How must consent be recorded?** Written evidence of consent is not legally required (but is considered good practice)

N.B. 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.

4.2. UK legal framework

The same **common law**¹² principles apply when seeking consent from patients for taking part in research as when seeking consent for treatment i.e. the patient **needs to understand in broad terms the nature and purpose of the procedure.**

In addition, the Department of Health advise that "*Case law on this issue is evolving. It is therefore advisable to inform the patient of any "material" or "significant" risks in the proposed treatment, any alternatives to it, and the risks incurred by doing nothing.*"¹³

¹² See GMC Consent guidance: Legal Annex - Common Law for more information: http://www.gmc-uk.org/guidance/ethical_guidance/consent_guidance_common_law.asp

¹³ Reference Guide to Consent for Examination or Treatment. (2009) Department of Health.

The GMC states that given that much research may not have direct benefits for the patients *“particular care” should be taken to ensure that possible research subjects have the fullest possible information about the proposed study and sufficient time to absorb it.*¹⁴

In general, any individual from whom consent is being sought:

- must be **competent** (able to understand, believe, retain and weigh the necessary information relevant to a particular decision and be able to communicate it)
- must have **sufficient information** to make a choice (e.g. an explanation of the nature and purpose of the research, what is proposed, the risks/benefits and alternatives for the participant etc.)
- must be able to give their consent **freely** (not pressured to take a decision with adequate time being given)

Obtaining the *written* consent of participants is NOT a legal requirement for research that is not a drug trial¹⁵. Nevertheless, for the majority of research it is considered best practice to do so¹⁶ and will usually be a requirement of REC approval

The Medicines for Human Use (Clinical Trials) Regulations 2004 (as amended) apply to clinical trials of medicines, often referred to as ‘drug trials’, (except where they are non-interventional trials). These regulations implement the EU Clinical Trials Directive (2001/20/EC) in UK law.

For CTIMPs consent (where provided by the participant or their legal representative) **must be documented *in writing* following an *interview* with a member of the investigating team.**

The only exception to this requirement is in the emergency research context where participants may be entered into a trial prior to consent being obtained from a legal representative under specific provisions¹⁷.

The Regulations require that the potential participant must:

- be informed of the **nature, significance, implications and risks** of the trial in **a prior ‘interview’ with the investigator, or another member of the investigating team**
- be informed of their **right to withdraw** from the trial at any time
- be provided with a **contact point to obtain further information** about the trial.

¹⁴ Ibid

¹⁵ Graeme Laurie and Emily Postan, ‘Rhetoric or Reality: What is the legal status of the consent form in health-related research?’ *Med Law Rev* 2013 21: 371-414

¹⁶ Boddington et al, ‘Consent forms in genomics: the difference between law and practice’ (2011) 18 (5) *European Journal of Health Law* 491, 517.

¹⁷ See

<http://www.mhra.gov.uk/Howweregulate/Medicines/Licensingofmedicines/Clinicaltrials/Legislation/ImplementationofClinicalTrialsDirectiveintheUK/index.htm>

- have their decision to take part **‘evidenced in writing, dated and signed, or otherwise marked, by that person so as to indicate his consent’**

Further information on the legal and governance framework for research in the UK can be found in the General Medical Council’s [legal annexes](#) to the ‘Good practice in research and consent to research’¹⁸ guidance.

The following paragraphs provide more details on some of the main documents in this area and their requirements.

4.3. Good Clinical Practice (GCP)

The GCP Directive ((Directive 2005/28/EC of 8 April 2005 of the European Parliament and of the Council)) defines Good Clinical Practice as “...a set of internationally recognised ethical and scientific quality requirements which must be observed for designing, conducting, recording and reporting clinical trials that involve the participation of human subjects.”

The principles of good clinical practice are outlined in articles 2 to 5 of the Directive and require that **clinical trials shall be conducted in accordance with the principles of the Declaration of Helsinki**.

The GCP Directive does not set out specific requirements for the information that should be provided to potential research participants. However, it does refer to the “**the ICH [International Conference on Harmonisation] Note for Guidance on Good Clinical Practice**”¹⁹ (also known as ‘ICH GCP’) and stipulates that, **whilst not mandatory, this guidance “should be taken into account”**:

The International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use, Guideline for Good Clinical Practice (ICH GCP) provides further guidance on the information that might be provided to potential participants as part of the consent process but **adherence to this guidance is not mandatory** and the participant information sheet should always be adapted, in a proportionate manner, to suit the specific study.

“Both the informed consent discussion and the written informed consent form and any other written information to be provided to subjects should include explanations of the following:

- (a) That the trial involves research.
- (b) The purpose of the trial.
- (c) The trial treatment(s) and the probability for random assignment to each treatment.
- (d) The trial procedures to be followed, including all invasive procedures.
- (e) The subject's responsibilities.
- (f) Those aspects of the trial that are experimental.

¹⁸ http://www.gmc-uk.org/guidance/ethical_guidance/research.asp

¹⁹ ICH Topic E 6, the ICH Note for Guidance on Good Clinical Practice is an international standard for GCP. It was adopted by the CPMP (CPMP/ICH/135/95) in July 1996 and became operational in the European Union (EU) in January 1997. The ICH Note for Guidance on GCP replaced the previous European Community GCP Guidelines, which were implemented in 1991.

- (g) The reasonably foreseeable risks or inconveniences to the subject and, when applicable, to an embryo, foetus, or nursing infant.
- (h) The reasonably expected benefits. When there is no intended clinical benefit to the subject, the subject should be made aware of this.
- (i) The alternative procedure(s) or course(s) of treatment that may be available to the subject, and their important potential benefits and risks.
- (j) The compensation and/or treatment available to the subject in the event of trial-related injury.
- (k) The anticipated prorated²⁰ payment, if any, to the subject for participating in the trial.
- (l) The anticipated expenses, if any, to the subject for participating in the trial.
- (m) That the subject's participation in the trial is voluntary and that the subject may refuse to participate or withdraw from the trial, at any time, without penalty or loss of benefits to which the subject is otherwise entitled.
- (n) That the monitor(s), the auditor(s), the IRB/IEC, and the regulatory authority(ies) will be granted direct access to the subject's original medical records for verification of clinical trial procedures and/or data, without violating the confidentiality of the subject, to the extent permitted by the applicable laws and regulations and that, by signing a written informed consent form, the subject or the subject's legally acceptable representative is authorizing such access.
- (o) That records identifying the subject will be kept confidential and, to the extent permitted by the applicable laws and/or regulations, will not be made publicly available. If the results of the trial are published, the subject's identity will remain confidential.
- (p) That the subject or the subject's legally acceptable representative will be informed in a timely manner if information becomes available that may be relevant to the subject's willingness to continue participation in the trial.
- (q) The person(s) to contact for further information regarding the trial and the rights of trial subjects, and whom to contact in the event of trial-related injury.
- (r) The foreseeable circumstances and/or reasons under which the subject's participation in the trial may be terminated.
- (s) The expected duration of the subject's participation in the trial.
- (t) The approximate number of subjects involved in the trial."

Research Governance Framework for Health and Social Care second edition, 2005

This document sets out the broad principle of good research governance for health and social care. There are different versions for all four UK nations. However, all versions include the following statement concerning GCP:

²⁰i.e. calculated according to the length of time involved or number of procedures that the participant has undergone in the event that they withdraw from the research early.

“The principles of Good Clinical Practice apply to all research involving patients, not just clinical trials.

(The Medical Research Council issued guidelines in 1998 for Good Clinical Practice in clinical trials in the public and charity sectors. The MRC guidelines apply the principles of Good Clinical Practice in the 1996 statement of the International Conference on Harmonisation (ICH GCP)).”

4.4. Declaration of Helsinki²¹

The **Declaration of Helsinki** (explicitly referred to in the Medicines for Human Use (Clinical Trials) Regulations²² which requires adherence to the “principles” of the declaration) echoes the provisions of the Clinical Trials Regulations in requiring that “*no competent individual may be enrolled in a research study unless he or she freely agrees*” but goes further in terms of the information to be delivered to the potential participant:

“24. In medical research involving competent human subjects, each potential subject must be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail, and any other relevant aspects of the study”

4.5. The Ottawa Statement on the Ethical Design and Conduct of Cluster Randomised Trials²³

The Ottawa Statement on the Ethical Design and Conduct of Cluster Randomized Trials is the output of an international, multidisciplinary consensus conference held in Ottawa, Canada from 28-30 November 2011.

The statement sets out 15 recommendations for the ethical design and conduct of CRTs. The recommendations provide guidance on the justification of a cluster randomised design, the need for REC review, the identification of research participants, obtaining informed consent, the role of gatekeepers in protecting group interests, the assessment of benefits and harms, and the protection of vulnerable participants.

The Statement is intended as guidance only. The consensus statement should be interpreted in light of the laws and regulations of the host country or countries, as well as other applicable international standards.

Recommendations 4 and 6 of the statement set out the requirement for informed consent unless waived by a REC under certain conditions:

Recommendation 4: Researchers must obtain informed consent from human research participants in a CRT, unless a waiver of consent is granted by a REC under specific circumstances.

²¹ WMA Declaration of Helsinki - Ethical Principles for Medical Research Involving Human Subjects (64th WMA General Assembly, Fortaleza, Brazil, October 2013) <http://www.wma.net/en/30publications/10policies/b3/>

²² “Clinical trials shall be conducted in accordance with the principles of the Declaration of Helsinki.” Schedule 1, Part 2, para. 6 - The Medicines for Human Use (Clinical Trials) Regulations 2004 (as amended)

²³ Weijer C, Grimshaw JM, Eccles MP, McRae AD, White A, et al. (2012) [The Ottawa Statement on the Ethical Design and Conduct of Cluster Randomized Trials](https://doi.org/10.1371/journal.pmed.1001346). PLoS Med 9(11): e1001346. doi:10.1371/journal.pmed.1001346

Recommendation 6: A REC may approve a waiver or alteration of consent requirements when (1) the research is not feasible without a waiver or alteration of consent, and (2) the study interventions and data collection procedures pose no more than minimal risk.

It should be noted that the Statement makes it clear that:

“An inappropriate reason to adopt a CRT [Cluster Randomised Trial] is the mistaken belief that the need to seek informed consent can be avoided by using cluster randomization.”; and

“If obtaining informed consent is feasible for some but not all study interventions or data collection procedures, then researchers should obtain separate informed consent, where possible, for each procedure.”

4.6. Future legislation: EU Clinical Trials Regulation²⁴

N.B. This Regulation does not currently apply to clinical trials conducted within the EU. It is currently anticipated to come into force in late 2016 / early 2017 and will replace both the existing European Clinical Trials and GCP Directives.

Once in force, the Clinical Trials Regulation will allow informed consent to be obtained by ‘**simplified means**’ in a very specific type of research known as a ‘**randomised cluster trial**’ [see Annex 1]. We need to consider what the practical and ethical implications of this important provision are now so that that we are able to provide appropriate guidance regarding the seeking of consent by simplified means once this Regulation is in force.

Randomised cluster trials are 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.

Under this Regulation researchers will be able to obtain informed consent by “**simplified means**”, without the traditional face-to-face discussion, provided that the following conditions are met:

- Trial is conducted in one member state
- No contradiction with national law
- Low intervention trial using licensed drugs
- Trial methodology requires groups of subjects (e.g. randomisation by GP practice or hospital) to be allocated to treatment rather than individuals
- No interventions other than standard treatment
- Protocol includes justification for gaining “informed consent by simplified means”.

Under this Regulation informed consent may be “deemed” to have been obtained if the potential subject, after being informed, does not object to participating in the clinical trial. This means that a patient could be included in the research unless they explicitly opt-out of taking part.

²⁴ Published in the Official Journal of the European Union on 27 May 2014 (<http://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=OJ:L:2014:158:FULL&from=EN>).

This represents a significant departure from the current UK Clinical trials Regulations/EU Clinical Trials Directive, which require the potential subject to have been **duly informed of the nature, significance, implications and risks** of the trial in a **prior interview with the investigator** or a member of the investigating team.

DRAFT

Annex 1

Articles 29 and 30 of the EU Regulation on Clinical Trials regarding 'informed consent' and 'cluster trials'

[N.B. *Shaded sections do not apply to cluster randomised trials conducted in accordance with Article 30*]

REGULATION (EU) No 536/2014 OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL of 16 April 2014 on clinical trials on medicinal products for human use, and repealing Directive 2001/20/EC

Article 29 Informed consent

1. Informed consent shall be written, dated and signed by the person performing the interview referred to in point (c) of paragraph 2, and by the subject or, where the subject is not able to give informed consent, his or her legally designated representative after having been duly informed in accordance with paragraph 2. Where the subject is unable to write, consent may be given and recorded through appropriate alternative means in the presence of at least one impartial witness. In that case, the witness shall sign and date the informed consent document. The subject or, where the subject is not able to give informed consent, his or her legally designated representative shall be provided with a copy of the document (or the record) by which informed consent has been given. The informed consent shall be documented. Adequate time shall be given for the subject or his or her legally designated representative to consider his or her decision to participate in the clinical trial.

2. Information given to the subject or, where the subject is not able to give informed consent, his or her legally designated representative for the purposes of obtaining his or her informed consent shall:

(a) enable the subject or his or her legally designated representative to understand:

(i) the nature, objectives, benefits, implications, risks and inconveniences of the clinical trial;

(ii) the subject's rights and guarantees regarding his or her protection, in particular his or her right to refuse to participate and the right to withdraw from the clinical trial at any time without any resulting detriment and without having to provide any justification;

(iii) the conditions under which the clinical trial is to be conducted, including the expected duration of the subject's participation in the clinical trial; and

(iv) the possible treatment alternatives, including the follow-up measures if the participation of the subject in the clinical trial is discontinued;

(b) be kept comprehensive, concise, clear, relevant, and understandable to a layperson;

(c) be provided in a prior interview with a member of the investigating team who is appropriately qualified according to the law of the Member State concerned;

(d) include information about the applicable damage compensation system referred to in Article 76(1); and

(e) include the EU trial number and information about the availability of the clinical trial results in accordance with paragraph 6.

3. The information referred to in paragraph 2 shall be prepared in writing and be available to the subject or, where the subject is not able to give informed consent, his or her legally designated representative.

4. In the interview referred to in point (c) of paragraph 2, special attention shall be paid to the information needs of specific patient populations and of individual subjects, as well as to the methods used to give the information.

5. In the interview referred to in point (c) of paragraph 2, it shall be verified that the subject has understood the information.

6. The subject shall be informed that the summary of the results of the clinical trial and a summary presented in terms understandable to a layperson will be made available in the EU database, referred to in Article 81 (the 'EU database'), pursuant to Article 37(4), irrespective of the outcome of the clinical trial, and, to the extent possible, when the summaries become available.

7. This Regulation is without prejudice to national law requiring that both the signature of the incapacitated person and the signature of his or her legally designated representative may be required on the informed consent form.

8. This Regulation is without prejudice to national law requiring that, in addition to the informed consent given by the legally designated representative, a minor who is capable of forming an opinion and assessing the information given to him or her, shall also assent in order to participate in a clinical trial.

Article 30 Informed consent in cluster trials

1. Where a clinical trial is to be conducted exclusively in one Member State, that Member State may, without prejudice to Article 35, and by way of derogation from points (b), (c), and (g) of Article 28(1), Article 29(1), point (c) of Article 29(2), Article 29(3), (4) and (5), points (a), (b) and (c) of Article 31(1) and points (a), (b) and (c) of Article 32(1), allow the investigator to obtain informed consent by the simplified means set out in paragraph 2 of this Article, provided that all of the conditions set out in paragraph 3 of this Article are fulfilled.

2. For clinical trials that fulfil the conditions set out in paragraph 3, informed consent shall be deemed to have been obtained if:

(a) the information required under points (a), (b), (d) and (e) of Article 29(2) is given, in accordance with what is laid down in the protocol, prior to the inclusion of the subject in the clinical trial, and this information makes clear, in particular, that the subject can refuse to participate in, or withdraw at any time from, the clinical trial without any resulting detriment; and

(b) the potential subject, after being informed, does not object to participating in the clinical trial.

3. Informed consent may be obtained by the simplified means set out in paragraph 2, if all the following conditions are fulfilled:

(a) the simplified means for obtaining informed consent do not contradict national law in the Member State concerned;

(b) the methodology of the clinical trial requires that groups of subjects rather than individual subjects are allocated to receive different investigational medicinal products in a clinical trial;

(c) the clinical trial is a low-intervention clinical trial and the investigational medicinal products are used in accordance with the terms of the marketing authorisation;

(d) there are no interventions other than the standard treatment of the subjects concerned;

(e) the protocol justifies the reasons for obtaining informed consent with simplified means and describes the scope of information provided to the subjects, as well as the ways of providing information.

4. The investigator shall document all refusals and withdrawals and shall ensure that no data for the clinical trial are collected from subjects that refuse to participate in or have withdrawn from the clinical trial.

Annex 2

Article 59(1) of Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to medicinal products for human use.

Article 59(1) sets out the six main sections of the patient information leaflet (PIL) and the information which must be included within each of these sections:

IDENTIFICATION OF THE MEDICINE

The name, the active substance(s), the pharmaceutical form, strength of the product should be stated.

THERAPEUTIC INDICATIONS

The conditions for which the medicine is authorised must be listed. This section should include any benefit information considered appropriate

INFORMATION NECESSARY BEFORE TAKING THE MEDICINE

Situations where the medicine should not be used, any precautions, warnings, interactions with other medicines or foods, information for special groups of patients (pregnant or nursing mothers), and any effects the medicine may have on the patient's ability to drive.

DOSAGE

How to take or use the medicine including both the route and method of administration, how often it should be given, how long the course of treatment will last, what to do if a dose is missed and if relevant what do in the event of an overdose and the risk of withdrawal effects.

DESCRIPTION OF SIDE EFFECTS

All the effects which may occur under normal use of the medicine and what action the patient should take if any of these occur. These should be listed by seriousness and then by frequency.

ADDITIONAL INFORMATION

This covers information on excipient details, a description of the product, registered pack sizes, storage conditions, name and address of the MAH and manufacturer

1. The package leaflet shall be drawn up in accordance with the summary of the product characteristics; it shall include, in the following order:

(a) for the identification of the medicinal product:

(i) the name of the medicinal product followed by its strength and pharmaceutical form, and, if appropriate, whether it is intended for babies, children or adults. The common

name shall be included where the product contains only one active substance and if its name is an invented name;

(ii) the pharmaco-therapeutic group or type of activity in terms easily comprehensible for the patient;

(b) the therapeutic indications;

(c) a list of information which is necessary before the medicinal product is taken:

(i) contra-indications;

(ii) appropriate precautions for use;

(iii) forms of interaction with other medicinal products and other forms of interaction (e.g. alcohol, tobacco, foodstuffs) which may affect the action of the medicinal product;

(iv) special warnings;

(d) the necessary and usual instructions for proper use, and in particular:

(i) the dosage,

(ii) the method and, if necessary, route of administration;

(iii) the frequency of administration, specifying if necessary the appropriate time at which the medicinal product may or must be administered;

and, as appropriate, depending on the nature of the product:

(iv) the duration of treatment, where it should be limited;

(v) the action to be taken in case of an overdose (such as symptoms, emergency procedures);

(vi) what to do when one or more doses have not been taken;

(vii) indication, if necessary, of the risk of withdrawal effects;

(viii) a specific recommendation to consult the doctor or the pharmacist, as appropriate, for any clarification on the use of the product;

(e) a description of the adverse reactions which may occur under normal use of the medicinal product and, if necessary, the action to be taken in such a case;

(f) a reference to the expiry date indicated on the label, with:

(i) a warning against using the product after that date;

(ii) where appropriate, special storage precautions;

(iii) if necessary, a warning concerning certain visible signs of deterioration;

(iv) the full qualitative composition (in active substances and excipients) and the quantitative composition in active substances, using common names, for each presentation of the medicinal product;

(v) for each presentation of the product, the pharmaceutical form and content in weight, volume or units of dosage;

(vi) the name and address of the marketing authorisation holder and, where applicable, the name of his appointed representatives in the Member States;

(vii) the name and address of the manufacturer;

(g) where the medicinal product is authorised in accordance with Articles 28 to 39 under different names in the Member States concerned, a list of the names authorised in each Member State;

(h) the date on which the package leaflet was last revised.

For medicinal products included in the list referred to in Article 23 of Regulation (EC) No 726/2004, the following additional statement shall be included 'This medicinal product is subject to additional monitoring'. This statement shall be preceded by the black symbol referred to in Article 23 of Regulation (EC) No 726/2004 and followed by an appropriate standardised explanatory sentence.

For all medicinal products, a standardised text shall be included, expressly asking patients to communicate any suspected adverse reaction to his/her doctor, pharmacist, healthcare professional or directly to the national spontaneous reporting system referred to in Article 107a(1), and specifying the different ways of reporting available (electronic reporting, postal address and/or others) in compliance with the second subparagraph of Article 107a(1).