



*National Patient Safety Agency*

National Research Ethics Service

**INFORMATION SHEETS**

**&**

**CONSENT FORMS**

**GUIDANCE FOR**

**RESEARCHERS & REVIEWERS**

**Version 3.2 May 2007**

## Introduction

It is clear that the public supports medical research and wishes it to continue ([Annex A](#)). This is not, however, an unquestioning acceptance and if researchers wish continuing public trust and participation, they need to demonstrate that their work is conducted to high ethical standards.

Potential participants need information upon which they can make their decisions. Empirical evidence indicates that, with occasional exceptions, they want to choose whether to participate only after the study has been explained to them ([Annex B](#)).

There is evidence, however, that participants' understanding is sometimes limited ([Annex C](#)) and hence our emphasis upon designing appropriate information ([Annex D](#)) which can help them make a decision.

Reflecting these considerations, the stipulation that researchers seek consent **after** providing appropriate information ([Annex B](#), [Annex D](#)) is a central theme in modern research ethics.

### What is the purpose of this guide?

We provide this document to guide researchers and reviewers alike, but there may be times when variation will be necessary. We do not wish to hinder improvement.

### Involving patients in research

It is good practice, and the Research Ethics Committee (REC) will look more favourably upon your application if you involve patients and representatives of the group likely to be recruited ([Annex E](#)).

### What is the place of the information sheet in obtaining consent?

We recognise that the information sheet is just one part of recruiting participants and the REC will wish to consider the whole process ([Annex F](#)).

We have tried to ensure this guidance meets the requirements of the ICH Good Clinical Practice (<http://www.ich.org/LOB/media/MEDIA482.pdf>), the European Clinical Trials Directive 2001/20/EC ([http://europa.eu.int/eur-lex/pri/en/oj/dat/2001/l\\_121/l\\_12120010501en00340044.pdf](http://europa.eu.int/eur-lex/pri/en/oj/dat/2001/l_121/l_12120010501en00340044.pdf)) and

the UK Medicines for Human Use (Clinical Trials) Regulation 2004 (<http://www.opsi.gov.uk/si/si2004/20041031.htm>). It should also be read in conjunction with the National Research Ethics Service (NRES) guidance on informed consent in clinical trials (<http://www.nres.npsa.nhs.uk/applicants/help/guidance.htm#consent>).

This document will be the subject of further 'Use, Comment and Revision'. If you wish, please send comments to [infosheets@nationalres.org.uk](mailto:infosheets@nationalres.org.uk) . We will also be trying to collect examples of good practice.

### **How can I use this guide?**

This guidance is divided into three main sections:

**Section One** provides general comments on information sheets for adults and children.

**Section Two** gives guidance for the design of information sheets for adults. An example of a consent form for adults is provided.

**Section Three** offers guidance for the design of information sheets for children and parents. In the final part of this section there is an example of a consent/assent form for children.

Supplementary information and references are provided in the Annexes, which the reader will be directed to in the text. You will find a list of all these, with hyperlinks, in the contents section on page 5. NRES would be pleased to receive comments and reference to other published work in these areas for further inclusion. If you wish to do so, please email [infosheets@nationalres.org.uk](mailto:infosheets@nationalres.org.uk).

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## 1. **SECTION ONE – General Comments on Information Sheets**

This section includes points to consider when designing information sheets for adults. Children's information sheets are covered in the next section, but we would advise researchers undertaking work involving children to read this section as well.

### 1.1 **Adults**

#### 1.1.1 **The process of obtaining consent**

Information sheets are only one part of the process of seeking informed consent. We would recommend researchers consider how best the research might be presented to potential participants ([Annex F](#)). You may therefore wish to explain this to a potential subject that it is important to take time to read the information sheet **with** the researcher obtaining consent (perhaps indicating how long this might take) and it is just as important then to have time for questions.

Your reasoning, choices, methods and media should be presented and explained to the REC.

#### 1.1.2 **One size will not fit all**

The level of detail should be appropriate to the nature of the study and the population to be studied. One size will not fit all so we suggest you match its length to the complexity and risk of your study. Studies with little or no intervention and hence less than minimal risk are likely to need a much shorter information sheet. You will not need to complete all sections, although if your trial is a Clinical Trial of an Investigational Medicinal Product ('drug trial') you will need to ensure you cover all ICH 'Elements of Informed Consent'.

#### 1.1.3 **Length**

There is concern that information sheets are becoming increasingly lengthy and complex. Where appropriate, the information sheet could be divided into two parts.

Part 1 should provide brief and clear information on the essential elements of the specific study: what the research is about, the condition or treatment under study, the

voluntary nature of involvement, what will happen during and after the trial, what treatment may be withheld, the participant's responsibilities, the potential risks, inconvenience or restrictions balanced against any possible benefits and the alternative(s). Part 1 should allow the participant to decide whether the study is of interest to them and whether they wish to read and discuss it further.

Part 2 should contain additional information on factors such as confidentiality and data protection, communication with the GP, indemnity and compensation, publication, etc., which should, of course, be read and understood before the participant decides whether they want to participate.

**BUT**, if appropriate it is entirely acceptable to produce a single section information sheet.

If it is a lengthy document a study summary, or 'Key Facts' section, at the beginning may help. It should not be the basis for consent however and it is worth considering how you could ensure the potential participant (if you include a summary) reads the full information sheet before considering consent.

Length does not always mean 'incomprehensibility'. Consider careful layout.

#### **1.1.4 Language/ writing style**

The tone should be invitational (the use of 'we' and 'you' may help). Obviously, it must not be coercive.

Write the information sheet in simple, non-technical terms that a lay person will understand easily. Try to use short words, sentences and paragraphs with clear subheadings to make the text manageable, and a font size for easy reading. If you intend to recruit elderly subjects you may need to use size 16 font.

For ease of reading, we recommend you use the active tense.

As a guide, the language level used should be no more difficult than that used in the information leaflets of medicines for the general public or in tabloid newspapers. Avoid large sections of unbroken text or long lists. Diagrams or pictures might be better.

Calculate the Flesch reading ease score, or an equivalent, and think how you might improve it.

Ask for comments from those who might be recruited or lay people ([Annex E](#)).

### **1.1.5 Presentation**

For the first page, use headed paper of the hospital/institution where the research is being carried out. Information sheets submitted to a REC may be headed simply on hospital/institution/GP Practice headed paper. If you are a local researcher for a REC approved study, the information sheet should be printed on local hospital/surgery paper (trial site) and must include the relevant local contact names and telephone numbers before it is used.

All consent forms and information sheets should be version dated in the header/footer to ensure the most recent is used, and pages numbered e.g. page 2 of 5.

### **1.1.6 Further guidance for participants**

There are many advisory documents in different media that might help potential participants find out more about research and decide whether they wish to participate. We would suggest you look through the available material to see what might help. You may wish to recommend or provide these for potential participants for additional background reading. It is important that you check material or websites that you direct your reader to ([Annex G](#)).

### **1.1.7 Other considerations**

There may be some issues where local requirements need to be included, e.g. radiation doses, alternative treatments. The Chief Investigator should make this clear in the submission to the main REC giving the single opinion.

If the researcher is not the participant's own 'health professional', consider how to distinguish research and clinical staff.

Consider whether any group in your study needs a different information sheet (such as a 'healthy comparator group').

Test your 'consent process'.

Ask for feedback from potential participants.

Consider whether you need to ask if subjects are already enrolled in a research project.

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## 1.2 Children

This section outlines some points to consider when designing information sheet for children. For general guidance on planning research that will involve children, please refer to [Annex H](#). These notes should be considered together with the points outlined in the 'adult' section.

### 1.2.1 Important points to consider

An information sheet should be designed for the appropriate age range to reflect their comprehension and development, for example:

- Children or young people 11-15 years;
- Children 6-10 years;
- Children 5 years and under.

There should also be an information sheet for parents or guardians.

Ideally such material should be shorter than that designed for adults.

It will help if you show your information sheets to some children of similar age before you submit the formal version to the REC.

**Consider the child's world.** It is important to indicate how the study will affect the child at home, school and his/her social activities.

### 1.2.2 Consent

Arrangements will vary according to the type of study proposed, ethical considerations and applicable law.

*Studies governed by the Medicines for Human Use (Clinical Trials) Regulations 2004 -*

Written consent must be given by parents or those with legal responsibility for the child, but children should also be asked for their assent, if appropriate.

Where the parent is competent to decide for their child but unable to read or write, an impartial witness could sign the consent form to say that the information sheet has been read by the parent and verbal consent has been given.

Studies **not** governed by the Medicines for Human Use (Clinical Trials) Regulations 2004 - UK law is untested with regard to the legal age of consent to take part *in research* (as opposed to treatment). It is possible to apply the principle of Gillick competence for research in the UK. This can be summarised that children who are felt to be competent to understand the research proposal and thus make decisions can give consent on their own behalf. It is unwise to use this for children younger than ten years of age.

In long term studies where the child may reach the age of majority, you will need to consider if it would be appropriate or feasible to obtain their consent to continue in the study or use samples already obtained.

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## **2. SECTION TWO – Guidance for design of information sheets for competent adults**

### **2.1 Part 1 of the information sheet**

This should provide brief and clear information on the essential elements of the specific study: what the research is about, the condition or treatment under study, the voluntary nature of involvement, what will happen during and after the trial, what treatment may be withheld, the participant's responsibilities, the potential risks, inconvenience or restrictions balanced against any possible benefits and the alternative(s). It should allow the participant to decide whether the study is of interest to them and whether they wish to read and discuss it further.

#### **2.1.1 Document heading**

It is recommended that the document be headed 'Patient Information Sheet', 'Participant Information Sheet' or 'Information about the research'.

#### **2.1.2 Study title**

Does this explain the study in simple English?

One consistent title should appear on all the documents and be self-explanatory to a lay person. The simplified title, given on the REC application form after the full title, is usually the most suitable. An appropriate protocol reference should appear on the information sheet and consent form, with the version number and date to permit cross-reference. If acronyms are used in the title they must be spelled out in full the first time they appear. The title should not consist of an acronym alone.

#### **2.1.3 Invitation paragraph**

You need to explain that you are asking the participant to take part in research. The following is an example:

*We would like to invite you to take part in a research study. Before you decide you need to understand why the research is being done and what it would involve for you. Please take time to read the following information carefully. Talk to others about the study if you wish.*

*(Part 1 tells you the purpose of this study and what will happen to you if you take part. Part 2 gives you more detailed information about the conduct of the study).*

*Ask us if there is anything that is not clear or if you would like more information. Take time to decide whether or not you wish to take part.*

*(You might wish to include one or two sentences explaining the study here. You might also wish to provide further information about research (Annex G)).*

#### **2.1.4 What is the purpose of the study?**

Purpose is an important consideration for subjects, and we recommend you present it clearly and succinctly, in context of other work in your field.

Projects may be primarily educational, and while this is entirely reasonable, this purpose should be made clear.

#### **2.1.5 Why have I been invited?**

You should explain briefly why and how (particularly if the approach is not by the health care worker) the participant was chosen and how many others will be in the study.

#### **2.1.6 Do I have to take part?**

You should explain that taking part in the research is entirely voluntary. The following is an example:

*It is up to you to decide. We will describe the study and go through this information sheet, which we will then give to you. We will then ask you to sign a consent form to show you have agreed to take part. You are free to withdraw at any time, without giving a reason. This would not affect the standard of care you receive.*

If further explanation is needed of other possible implications of withdrawal, this should be given in Part 2.

### **2.1.7 What will happen to me if I take part?**

To answer this question, try to 'put yourself in the subject's shoes.'

This section should include:

- how long the participant will be involved in the research;
- how long the research will last (if this is different);
- how often they will need to attend, meet a researcher, visit a clinic or their GP surgery (if this is appropriate);
- how long these visits will be;
- what exactly will happen e.g. access to personal information/samples questionnaire, interview, discussion group, measurement, sample collection, blood tests, x-rays, etc.

Use the most appropriate format (tables, diagrams, photos etc). The detail required will depend on the complexity of the study. It may help if the information is displayed in a simple flowchart or grid indicating what will happen at each visit rather than lengthy lists in the text.

It should be clear which procedures are over and above those involved in standard diagnosis, treatment or management.

It is also essential to explain whether any normal treatment will be withheld for all or part of the study.

Long-term monitoring/follow-up should be mentioned.

If the study will involve video/audio-taping or photography, you should explain what is intended, including the confidentiality issues. Specific consent will be needed if material of any sort will be published if it identifies the subject.

You should set out simply the research methods you intend to use. The following simple definitions may help:

**Randomised Trial ([Annex I](#))**

*Sometimes we don't know which way of treating patients is best. To find out, we need to compare different treatments. We put people into groups and give each group a different treatment. The results are compared to see if one is better. To try to make sure the groups are the same to start with, each patient is put into a group by chance (randomly).*

*(You should tell the patients what chance they have of getting the study drug/treatment.)*

**Blind trial**

*In a 'blind trial' you will not know which treatment group you are in. If the trial is a 'double blind trial', neither you nor your doctor will know in which treatment group you are (although, if your doctor needs to find out he/she can do so).*

**Cross-over trial**

*In a 'cross-over trial' the groups each have the different treatments in turn. There may be a break between treatments so that the first drugs are cleared from your body before you start the new treatment.*

**Placebo ([Annex J](#))**

*A placebo is a 'dummy treatment', which looks like the genuine medicine but contains no active ingredient.*

**2.1.8 Expenses and payments ([Annex K](#))**

You should explain if expenses (e.g. travel, meals, child-care, compensation for loss of earnings, etc.) are available.

You should consider whether any vouchers, gifts, etc., which you are intending to give as a 'thank-you' for participation, should be detailed in the information sheet.

The arrangements for any other payment, e.g. for Phase I volunteers, should be given, including, if necessary, an explanation of how payments may be influenced by the duration of involvement in a study or factors such as the completeness of diaries.

### **2.1.9 What will I have to do?**

Set down briefly and clearly what you will expect of your research subjects.

Medical studies: Explain (if appropriate) that the participants should take the study medication regularly as directed and whether they can continue to take their regular medication or other prescribed or over-the-counter drugs. It should also be explained that they will need to consider whether they should participate if they are currently involved in other drug studies, or have been in the recent past (specify how long). Explain other essential study requirements, e.g. attendance at all scheduled visits, keeping diaries, filling questionnaires, etc.

Any lifestyle, medical health product or dietary restrictions should be stated.

### **2.1.10 What is the drug, device or procedure that is being tested?**

You should include a short description of the drug, device or procedure and give the stage of development. You should, when appropriate, state the dosage of the drug and method of administration. Details are needed of any contraindicated drugs, including over-the-counter drugs.

### **2.1.11 What are the alternatives for diagnosis or treatment?**

For therapeutic research the participant should be told what other managements are available, with the important comparative risks and benefits.

For a multi-site study, the Chief Investigator should check on local variations in alternative treatments, which may need to be reflected in the information given to the main REC for approval. Relevant information can then be drawn to the attention of participants at each trial site.

### **2.1.12 What are the possible disadvantages and risks of taking part? ([Annex L](#), [Annex M](#))**

Any risks, discomfort or inconvenience should be briefly outlined. However, explanation of risk is notoriously difficult, and researchers should consider carefully **how** to explain any risk in their study. The published literature should be consulted and material presented to likely participant groups to assess its value.

In designing the information sheet you should consider insurance issues and whether patients should be informed that their participation may affect insurance cover.

If it is a possibility, the potential participant should be told what would happen if other conditions were discovered of which he or she was unaware ([Annex N](#)).

A separate section on possible information sheets for genetic research is given in [Annex O](#).

### **2.1.13 What are the side effects of any treatment received when taking part?**

For any drug or procedure you should explain the possible side effects. For any new drug it should be explained that there might be unknown side effects. International Commission on Harmonisation Good Clinical Practice (ICH GCP) requires participants to be told about 'reasonably foreseeable risks.'

Side effects should be listed in terms the participant will clearly understand (e.g. 'damage to the heart' rather than 'cardiotoxicity'; 'abnormalities of liver tests' rather than 'raised liver enzymes').

The information should be prioritised in terms of seriousness, severity and frequency, with a simple example of frequency, which a participant would understand. It should reflect what a reasonable person would expect to be mentioned (i.e. rare side effects are relevant if they may be serious or permanent). The level of detail should also be influenced by the expected benefit from the treatment and the underlying prognosis of the condition.

For a very new or very potent investigational drug, a fuller list of suspected side-effects may be appropriate.

Adverse events that have been noted with an equal rate in active and control groups and that are most likely due to the underlying condition should not usually be listed as likely side effects.

If participants suffer these or any other symptoms they should be given clear guidance on when, how and to whom to report them. Contact numbers should be given clearly and boldly under section 16.

#### **2.1.14 Ionising Radiation (Medical Exposure) Regulations – IRMER**

If the use of additional ionising radiation is required as part of the research study, then information must be given to the participant on the radiation involved, in everyday terms that they can understand ([Annex P](#)).

Since treatments may differ at individual sites in a multi-site study, expert local advice must be sought for each site. The Chief Investigator should check on local variations so that the range can be reflected in the information given to the main REC for approval. Relevant information can then be drawn to the attention of participants at each trial site.

#### **2.1.15 Harm to the unborn child: therapeutic studies ([Annex Q](#))**

Complete this section carefully. In certain circumstances its use would be inappropriate.

##### **For women**

A clear warning must be given in studies where there could be harm to an unborn child or there was risk in breast-feeding. The information should include the need for pregnancy testing, contraceptive requirements, and reporting of a pregnancy during the trial. If any pregnancy were to be monitored, this needs to be made clear, particularly if the mother's notes or child's notes are going to be accessed. If the baby will be followed up or examined post-natally, this should also be explained.

##### **For men**

There should also be an appropriate warning and advice for men if the treatment could damage sperm and consequently the foetus. Information concerning the importance of careful contraception and what to do if their partner becomes pregnant is essential. Specific advice for pregnant partners may be needed, including information on any compensation arrangements.

Examples of possible wording are given in [Annex Q](#).

### **2.1.16 What are the possible benefits of taking part? ([Annex R](#))**

Explain these, but where there is no intended clinical benefit, this should be stated clearly. It is important not to exaggerate the possible benefits. It would be reasonable to say something similar to:

*We cannot promise the study will help you but the information we get from this study will help improve the treatment of people with (name of condition).*

Separation of risks, benefits and purpose of the study may sometimes lead to a loss of clarity about the balance of risk and benefit. In such cases, risks and benefits should be sensibly linked.

### **2.1.17 What happens when the research study stops? ([Annex S](#))**

The arrangements after a therapeutic trial must be given, particularly if this differs from that normally expected for their medical condition. It must be clear whether the participant will have continued access to any benefits or intervention they may have obtained during the research. If the treatment will not be available after the research finishes, this should be explained to the participant with information on what treatment will be available instead.

You should consider whether and when it may be possible to tell participants which arm of the study they were in.

### **2.1.18 What if there is a problem?**

A short statement could be given here, for example:

*Any complaint about the way you have been dealt with during the study or any possible harm you might suffer will be addressed. The detailed information on this is given in Part 2.*

### 2.1.19 Will my taking part in the study be kept confidential? ([Annex T](#))

A short general statement can be given here, for example:

*Yes. We will follow ethical and legal practice and all information about you will be handled in confidence. The details are included in Part 2.*

This completes part I.

*If the information in Part 1 has interested you and you are considering participation, please read the additional information in Part 2 before making any decision.*

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## 2.2 Part 2 of the information sheet

### What if relevant new information becomes available?

You will need to tell the participant about this. The following is an example:

*Sometimes we get new information about the treatment being studied. If this happens, your research doctor will tell you and discuss whether you should continue in the study. If you decide not to carry on, your research doctor will make arrangements for your care to continue. If you decide to continue in the study he may ask you to sign an updated consent form.*

*If this happens, your research doctor might consider you should withdraw from the study. He/she will explain the reasons and arrange for your care to continue.*

*If the study is stopped for any other reason, we will tell you and arrange your continuing care.*

### 2.2.1 What will happen if I don't want to carry on with the study?

Explain what the subject can and can't expect if he or she withdraws. It may not be possible or desirable for data to be extracted and destroyed.

In a clinical trial, the participant may wish to withdraw entirely or may wish to withdraw from treatment but be willing to continue to be followed up. If there are any restrictions on withdrawal, e.g. a single intervention will take place but they may withdraw from any further data collection, this should be made clear. If continuing follow-up is genuinely in the participant's own interests or an 'exit' check up will be needed, then this should be stated. The participant, however, retains the right to decide if data from this visit can be used.

The position on retention/destruction of data/samples on withdrawal must be made clear ([Annex U](#)). In a clinical trial it is usually important to retain data already collected, and may be important to collect further outcome data on an 'intention to treat' basis. It is important to make your intentions clear to the participant, and ask for the relevant consent, for example:

*If you withdraw from the study, we will destroy all your identifiable samples, but we will need to use the data collected up to your withdrawal.*

*Or*

*You can withdraw from treatment but keep in contact with us to let us know your progress. Information collected may still be used. Any stored blood or tissue samples that can still be identified as yours will be destroyed if you wish.*

### **2.2.2 What if there is a problem?**

You should inform patients how complaints will be handled and what redress may be available. This must be applicable, as appropriate, to NHS and private settings for the research.

#### **Complaints**

A contact number should be given. This may be the researcher, who can try to solve the problem in the first instance. However, a participant may not wish to complain to the researcher if he/she is the object of the complaint, and may wish to make a more formal complaint.

*If you have a concern about any aspect of this study, you should ask to speak to the researchers who will do their best to answer your questions (contact number). If you remain unhappy and wish to complain formally, you can do this through the NHS Complaints Procedure (or Private Institution). Details can be obtained from the hospital.*

#### **Harm**

Appropriate redress and/or compensation should be available and details of insurance/indemnity schemes should be given.

#### **NHS based research**

NHS bodies are liable for clinical negligence and other negligent harm to individuals covered by their duty of care. NHS Institutions employing researchers are liable for negligent harm caused by the design of studies they initiate. The provision of such indemnity for negligent harm should be stated to the participant.

*In the event that something does go wrong and you are harmed during the research and this is due to someone's negligence then you may have grounds for a legal action for compensation against (name of Sponsor Organisation, NHS Trust, Private Clinic) but you may have to pay your legal costs. The normal National Health Service complaints mechanisms will still be available to you (if appropriate).*

NHS Indemnity does not offer no-fault compensation i.e. for non-negligent harm, and NHS bodies are unable to agree in advance to pay compensation for non-negligent harm. They are able to consider an ex-gratia payment in the case of a claim. The REC, however, is required to consider in each trial whether it is acceptable to seek consent without no-fault compensation, given the risks. If a study (as considered by the approving REC) carries a significant risk of serious non-negligent harm from study procedures required by the protocol, then the Chief/Principal investigators should obtain agreement from their employers for statements on how this might be handled and suitable wording included in the information sheet.

For a Pharmaceutical industry sponsored trial, where there are The Association of the British Pharmaceutical Industry (ABPI), or other no-fault compensation arrangements, the following (or similar) should be included:

*We will provide compensation for any injury caused by taking part in this study in accordance with the guidelines of the Association of the British Pharmaceutical Industry (ABPI).*

*We will pay compensation where the injury probably resulted from:*

*A drug being tested or administered as part of the trial protocol*

*Any test or procedure you received as part of the trial*

*Any payment would be without legal commitment. (Please ask if you wish more information on this)*

*We would not be bound by these guidelines to pay compensation where:*

*The injury resulted from a drug or procedure outside the trial protocol*

*The protocol was not followed.*

It is expected that ABPI guidelines require cover for all study procedures carried out in accordance with the protocol. Universities and other public bodies employing

researchers have vicarious liability for their actions, and are expected to insure against risk of claims relating to clinical trials that their staff design and undertake. They may have clinical trials insurance that covers both negligence and no-fault compensation; this would normally exclude clinical negligence for which NHS bodies are liable. Appropriate statements should be included in the information sheet.

### 2.2.3 Will my taking part in this study be kept confidential? [\(Annex T\)](#)

You should tell the participant how their confidentiality will be safeguarded during and after the study.

You may wish to tell the participants how your procedures for handling, processing, storage and destruction of their data match the Caldicott principles and/or the Data Protection Act 1998.

The participant should be told:

- how their data will be collected;
- that it will be stored securely, giving the custodian and level of identifiability (e.g. coded, anonymous, etc – (the definitions given in the MRC guidelines are suitable);
- what it will be used for. It must be clear if the data is to be retained for use in future studies and whether further REC approval will be sought;
- who will have access to view identifiable data (authorised persons such as researchers, sponsors, regulatory authorities & R&D audit (for monitoring of the quality of the research) etc (not normally RECs in the UK);
- how long it will be retained and that it will be disposed of securely ([Annex U](#)).

A suggested form of words that you may wish to include for drug company sponsored research is:

*If you join the study, some parts of your medical records and the data collected for the study will be looked at by authorised persons from the company sponsoring and/or the company organising the research. They may also be looked at by people from the company, by representatives of regulatory authorities and by authorised people to check that the study is being carried out correctly. All will have a duty of confidentiality to you as a research participant and we will do our best to meet this duty.*

*Or for other research:*

*All information which is collected about you during the course of the research will be kept strictly confidential, and any information about you which leaves the hospital/surgery will have your name and address removed so that you cannot be recognised (if it is applicable to your research).*

Participants have the right to check the accuracy of data held about them and correct any errors.

Participants should be informed of any transfer of their identifiable data to countries having a lower standard of data protection than the UK.

The following or similar words could be used:

*Data collected during the study may be sent to associated researchers to countries where the laws don't protect your privacy to the same extent as the Data Protection Act in the UK but the company will take all reasonable steps to protect your privacy.*

#### **2.2.4 Involvement of the General Practitioner/Family doctor (GP)**

You should explain if the participant's GP (or other health care practitioner) needs to be notified of their participation, and seek consent. You should explain what information will be exchanged.

There may be circumstances in which informing the GP may not be necessary, acceptable or possible.

#### **2.2.5 What will happen to any samples I give? ([Annex V](#))**

It should be clear to the participant, in the description of study procedures whether:

- new samples will be taken (e.g. blood, tissue, specifically for this study);
- samples excess to a clinical procedure will be asked for;
- access to existing stored samples will be asked for.

The same type of information, as for data, is needed. This should include:

- the secure procedures for collecting, using and storing samples;
- any possible intended use in the future for research that cannot yet be specified. A separated or two part consent form is recommended if future use is intended, and it should be clear if further REC approval will be sought;
- who will have access;
- the level of identifiability (for this study and for storage for future studies);
- provision for destruction;
- procedures for possible feedback of individually significant information from their use;
- Whether samples will be transferred outside the UK.

A commonly accepted concept, 'the sample as a 'Gift'' has been proposed by the Medical Research Council (UK). If this is how researchers wish to see collection of samples, it will need to be explained to the subject.

#### **2.2.6 Will any genetic tests be done?**

Guidance is given in [Annex O](#).

A separate consent form for genetic studies should be used to allow participants to take part in the main study alone without joining a genetic sub-study, unless this is a necessary condition of trial entry.

#### **2.2.7 What will happen to the results of the research study? ([Annex W](#), [Annex X](#))**

Participants often want to know results of a study they have been in.

The results could be separated into 'broad scientific results of a trial' and 'results with relevance to the individual'. Consider both as appropriate, but they may need different management.

You should tell the patients what will happen to the results of the research, whether it is intended to publish the results and how the results will be made available to participants. You should add that they will not be identified in any report/publication unless they have given their consent.

### 2.2.8 Who is organising and funding the research?

The answer should include the organisation or company sponsoring the research and funding the research if these are different (e.g. Medical Research Charity, Pharmaceutical Company or academic institution).

The patient should be told whether the doctor conducting the research is being paid for including and looking after the patients in the study. This means payment other than that to cover necessary expenses such as laboratory tests arranged locally by the researcher, or the costs of a research nurse. The following is an example:

*The sponsors of this study will pay (name of hospital department or research fund) for including you in this study.*

*Or*

*Your doctor will be paid for including you in this study.*

### 2.2.9 Who has reviewed the study?

*All research in the NHS is looked at by independent group of people, called a Research Ethics Committee to protect your safety, rights, wellbeing and dignity. This study has been reviewed and given favourable opinion by \_\_\_\_\_ Research Ethics Committee.*

The information sheet should be dated and given a version number (referring to a protocol number if necessary).

The information sheet should state that the patient will be given a copy and a signed consent form to keep.

### 2.2.10 Further information and contact details ([Annex G](#))

Participants may want further information. This could be subdivided:-

1. General information about research.
2. Specific information about this research project.
3. Advice as to whether they should participate.
4. Who they should approach if unhappy with the study.

You should give the participant an appropriate contact point for any or all these categories. For (1) this may be information from documents or websites. It is likely that (2) will need to be provided by someone in the research team. Similarly (3) might be provided by members of the team but other possibilities might be one of the potential participant's health care professionals. This can be your name or that of another doctor/nurse involved in the study.

You should also provide a contact number if a subject had any concerns during the study, if this is different. For some studies an emergency contact number (which will be manned out-of-hours), if different, should be given and clearly displayed.

In a multi-site trial, the numbers must be appropriate for each site.

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## 2.3 The Consent Form

The example of the [consent form](#) given below is toward the minimum requirement, which will be suitable for many studies but may need alterations to be commensurate with your study, sections 3 and 4 may not be relevant to some. The participant is consenting to everything described in the text of the information sheet.

For some studies a fuller itemised or hierarchical consent form may be needed to cover important issues, especially if additional elements are optional for the participant. These may include:

- additional invasive tests or samples required for study purposes only;
- consent to use of audio/video-taping, with possible use of verbatim quotation or use of photographs;
- transfer of data/samples to countries with less data protection;
- agreement to receive individual feedback from testing.

The signatories to the consent should be those who are involved in the consent process, e.g. the participant, the researcher or a representative of the researcher delegated to take consent.

An independent witness is not routinely required except in the case of consent by a participant who may be blind, illiterate etc.

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(Form to be on headed paper)

Centre Number:

Study Number:

Patient Identification Number for this trial:

**CONSENT FORM**

Title of Project:

Name of Researcher:

Please initial  
box

- 1. I confirm that I have read and understand the information sheet dated.....  
(version.....) for the above study. I have had the opportunity to consider the information,  
ask questions and have had these answered satisfactorily.
- 2. I understand that my participation is voluntary and that I am free to withdraw at any time  
without giving any reason, without my medical care or legal rights being affected.
- 3. I understand that relevant sections of my medical notes and data collected during the study,  
may be looked at by individuals from [company name], from regulatory authorities or from the  
NHS Trust, where it is relevant to my taking part in this research. I give permission for these  
individuals to have access to my records.
- 4. I agree to my GP being informed of my participation in the study
- 5. I agree to take part in the above study.

\_\_\_\_\_  
Name of Patient                      Date                      Signature

\_\_\_\_\_  
Name of Person                      Date                      Signature  
taking consent

When completed, 1 for patient; 1 for researcher site file; 1 (original) to be kept in medical notes

## 2.4 Consent

Detail needs to be commensurate with the study.

The principles of International Commission on Harmonisation – Good Clinical Practice (ICH GCP) guide trials of investigational medicinal products.

‘Freely given informed consent should be obtained from every subject prior to clinical trial participation.’

This is defined as,

‘A subject voluntarily confirms his or her willingness to participate in a particular trial, after having been informed of all aspects of the trial that are relevant to the subject’s decision to participate. Informed consent is documented by means of a written, signed and dated informed consent form.’

Consent can be taken by the Investigator or person designated.

The ICH GCP elements of Informed Consent are:

The information for participants should include:

- the study title and an invitation to participate;
- the trial involves research;
- the purpose of the study;
- why the participant has been chosen;
- the voluntary nature of participation and participants may withdraw from the trial at any time without penalty or loss of benefits to which they were otherwise entitled;
- the trial treatment(s) and the probability for random assignment to each treatment;
- the trial procedures to be followed, including all invasive procedures;
- those aspects of the trial that are experimental;
- the alternative procedure(s) or course(s) of treatment that may be available to the subject, and their important potential benefits and risks;
- the approximate number of participants involved in the trial;

- the participants responsibilities in the study, including the expected duration of their participation in the trial;
- the reasonably foreseeable risks or inconveniences to the subject, including specific risks on ionising radiation or pregnancy during the trial;
- the reasonably expected benefits. When there is no intended clinical benefit to the participant, they should be made aware of this;
- the subject or the subject's legally acceptable representative will be formed in a timely manner if information becomes available that may be relevant to the subject's willingness to continue participation in the trial;
- the foreseeable circumstances and/or reasons under which the subject's participation in the trial may be terminated;
- care after the trial has stopped;
- the compensation and/or treatment available to the subject in the event of trial related injury;
- 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;
- details of anticipated prorated payments and expenses, if any, for participating in the trial and any other arrangements for payment, including an explanation of how payment may be influenced by duration of participation or completion of diaries etc.;
- assurance 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;
- what participants should do if they have a problem or a complaint regarding the trial;
- contact details are clearly stated.

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### **3. SECTION THREE – Guidance for design of information sheets for children/young people**

#### **3.1 Information sheets for children / young people aged 11 to 15 ([Annex H](#))**

This should be read alongside Section One ‘General comments on information sheets for adults’ and Section Two ‘Guidance for design of information sheets for competent adults.’

##### **3.1.1 Part 1 of the information sheet**

This section should help to give you first thoughts about the project.

##### **3.1.2 Study title**

Is the title self explanatory to a young person? If not, give a short title that is easily understood.

##### **3.1.3 Invitation paragraph**

This should explain briefly what research is and that the young person is being asked to take part in a research study. The following is a suitable example:

*We are asking if you would take part in a research project to find the answer to the question...(insert your research question).  
Before you decide if you want to join in it's important to understand why the research is being done and what it will involve for you. So please consider this leaflet carefully. Talk about it with your family, friends, doctor or nurse if you want to.*

##### **3.1.4 Why are we doing this research?**

The background and aim of the study should be given briefly here.

##### **3.1.5 What is the medicine, device or procedure that is being tested?**

You should include a short description of the medicine or device.

### 3.1.6 Why have I been invited to take part?

You should explain:

- how the young person was chosen;
- how many other children will be studied in this project;
- how many children have previously been studied for this medicine/device.

If the research is on a specific disease this should be explained so they understand why they have been chosen, for example:

*You have been invited to join our study because you have asthma... 3000 young people have already helped test this medicine and this project will involve a further 5000 from seven countries.*

### 3.1.7 Do I have to take part?

You should explain that taking part in the research is entirely voluntary. You could use the following paragraph:

*No. It is up to you. If you do, your doctor will ask you to sign a form giving your consent or assent. You will be given a copy of this information sheet and your signed form to keep. You are free to stop taking part at any time during the research without giving a reason. If you decide to stop, this will not affect the care you receive.*

### 3.1.8 What will happen to me if I take part?

This section should include:

- how long the young person will be involved in the research;
- how long the research will last (if this is different);
- how often they will need to attend, meet a researcher, visit a clinic or their GP surgery (if this is appropriate);
- how long these visits will be;
- what exactly will happen e.g. access to personal information/samples, questionnaire, interview, discussion group, measurement, sample collection, blood tests, x-rays, etc.

Use the most appropriate format (tables, diagrams, photos etc.). The detail required will depend on the complexity of the study. It may help if the information is displayed in a simple flowchart or grid indicating what will happen at each visit rather than lengthy lists in the text.

You should make clear which procedures are experimental and which procedures are over and above those involved in standard care.

It is also essential to explain whether any normal treatment will be withheld for all or part of the study.

Long-term monitoring/follow-up should be mentioned.

### **3.1.9 What will I be asked to do?**

Explain the parent's and child's responsibilities, set down clearly what you expect of them.

Explain clearly all study related procedures and schedules. It should be made clear what their responsibilities are during the trial, especially if they have to do anything at home e.g. diary cards.

Explain (if appropriate) that medicine must be taken regularly, if there are there any lifestyle or dietary restrictions and if they can take their usual medicines.

Explain also any consequences that might affect schooling.

### **3.1.10 What other medicines could I have instead?**

For therapeutic research the young person should be told in easy language what other treatments are available.

### **3.1.11 What are the side effects of the medicines and might I have some if I take part in the research?**

For any new drug or procedure you should explain the possible side effects and what would be the appropriate action to take. You should give them a contact name and

number if they or their parents become concerned and a name and number to contact in the event of an emergency (if that is different).

The known side effects should be listed in terms that are understandable. For any new drug it should be explained that there may be unknown side effects.

### **3.1.12 Is there anything else to be worried about if I take part?**

(Issues such as pregnancy testing are covered in [Annex Q.](#))

If the use of additional ionising radiation is required as part of the research study, then information must be given to the young person on the additional amount of radiation involved, in terms that they can understand (Annex P).

### **3.1.13 What are the possible benefits of taking part?**

If there are benefits these can be stated but should not be coercive. Where there is no intended clinical benefit, this should be stated clearly.

*We cannot promise the study will help you but the information we get might help treat young people with (name of condition) with better medicines in the future.*

### **3.1.14 Contact details**

You should give the young person and parents a contact point for further information. This can be your name or that of another doctor/nurse involved in the study. It is important that contact numbers are kept up to date.

**Thank you for reading so far – if you are still interested, please go to Part 2:**

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## **3.2 Part 2 of the information sheet**

More detail – information you need to know if you still want to take part.

### **3.2.1 What happens when the research project stops?**

If the treatment will not be available after the research finishes this should be explained carefully. You should also explain what treatment will be available instead.

### **3.2.2 What happens if new information about the research medicine comes along?**

You could use something like the following:

*Sometimes during research, new things are found out about the research medicine. Your doctor will tell you all about it if this happens. What is best for you might be:*

*To carry on as before*

*To stop taking part and go back to your usual treatment.*

### **3.2.3 What if there is a problem or something goes wrong?**

You will need to explain what will happen in such an eventuality.

### **3.2.4 Will anyone else know I'm doing this?**

You should explain that all information collected will be kept confidential, and what this means. A suggested form of words is:

*We will keep your information in confidence. This means we will only tell those who have a need or right to know. Wherever possible, we will only send out information that has your name and address removed.*

You should explain if applicable, that for studies not being conducted by a GP, the young person's own GP, or other carers treating the child, will be notified of their participation.

### 3.2.5 What will happen to any samples I give?

A commonly accepted concept, the 'sample as a 'Gift'' has been proposed by the MRC (UK). If this is how researchers wish to see collection of samples, it will need to be explained.

It should be clear in the description of study procedures whether:

- new samples will be taken (e.g. blood, tissue, specifically for this study);
- samples excess to a clinical procedure will be asked for;
- access to existing stored samples will be asked for.

The same type of information, as for data, is needed. This should include:

- the security procedures for collecting, using and storing samples;
- any possible intended use in the future for research that cannot yet be specified; A separated or two part consent form is recommended if future use is intended, and it should be clear if further REC approval will be sought;
- who will have access;
- the level of confidentiality (for this study and for storage for future studies);
- provision for destruction;
- procedures for possible feedback of individually significant information from their use;
- whether samples will be transferred outside the UK.

### 3.2.6 Genetic tests (Only include heading if relevant)

Guidance is given in [Annex O](#).

### 3.2.7 Who is organising and funding the research?

The answer should include the organisation or company sponsoring or funding the research. The young person should be told whether the doctor conducting the research is being paid for including and looking after the patient in the study. You could say:

*The organisers of this project will pay (name of hospital department or research fund) for including you in this study.*

Or

*Your research doctor will be paid for including you in this study.*

### **3.2.8 Who has reviewed the study?**

You may wish to say something like:

*Before any research goes ahead it has to be checked by a Research Ethics Committee.*

*They make sure that the research is fair. Your project has been checked by the*

*\_\_\_\_\_ Research Ethics Committee.*

*Thank you for reading this – please ask any questions if you need to.*

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### **3.3 Information sheets for children aged 6 to 10 years**

It is unlikely that the children in this age group will be asked to consent, but the study should be explained so the child can consider assent. The information form can therefore be much shorter, with an explanation that their parents will be asked for consent.

#### **3.3.1 Study title**

This should be in very simple, clear terms.

#### **3.3.2 What is research? Why is this project being done?**

Give a brief definition of research and state clearly and simply why your research is being done.

*Research is a way we try to find out the answers to questions. We want to see if Medicine X treats (asthma) better than Medicine Y.*

#### **3.3.3 Why have I been asked to take part?**

#### **3.3.4 Did anyone else check the study is OK to do?**

*Before any research is allowed to happen, it has to be checked by a group of people called a Research Ethics Committee. They make sure that the research is fair. Your project has been checked by the \_\_\_\_\_ Research Ethics Committee.*

#### **3.3.5 Do I have to take part?**

You should explain very simply that taking part in the research is entirely voluntary.

#### **3.3.6 What will happen to me if I take part in the research?**

A simple flow diagram or timetable may help.

How many visits will there be and will the child need to miss any school?

Procedures need simple, non-frightening explanations.

**3.3.7 Is there another sort of medicine I can have instead?**

Briefly explain what the alternatives are for diagnosis/treatment/procedure so that the research is not given as their only option.

**3.3.8 Will the medicine upset me?**

Any side effects need to be explained in simple language.

**3.3.9 Might anything else about the research upset me?**

Simple, sensitive explanations are needed to prepare the child and you should also say how they can be alleviated.

**3.3.10 Will joining in help me?**

*We cannot promise the study will help you but the information we get might help treat young people with (name of condition) with better medicines in the future.*

**3.3.11 What happens when the research stops?**

State briefly but clearly what will happen afterwards: *negotiate*:

- will the study medicine still be available?
- will the child go back to previous treatment?

**3.3.12 What if something goes wrong during the project?**

You will need to explain what will happen in such an eventuality, but complicated lengthy wording is unnecessary as this is in the parent information sheet.

**3.3.13 Will my medical details be kept private if I take part? Will anyone else know I'm doing this?**

In simple terms you will need to explain that others will not know of the child's participation unless it is necessary.

### **3.3.14 What happens if a better medicine comes along?**

There should be a simple statement that if better, proven treatment is developed, taking part in this study will not stop him/her getting it.

### **3.3.15 What if I don't want to do the research anymore?**

State that a child or parent can opt out at any time, and give reassurance that the doctor will discuss other treatments with child and parents.

*If at any time you don't want to do the research anymore, just tell your parents, doctor or nurse. They will not be cross with you. Your doctor will help you decide which medicine is best to use afterwards.*

### **3.3.16 What if something goes wrong?**

You will need to explain what will happen in such an eventuality, but complicated lengthy wording should be avoided as this is in the parent information sheet.

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### **3.4 Information for children five years and under**

This should be predominantly pictorial, with very simple sentences to be shown/read to the child.

It should say at the top that it is intended to be shown/read to the child by their parent/guardian.

Protocols could be supported by videos, or audio-tapes.

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## POSSIBLE ASSENT FORM FOR CHILDREN

(to be completed by the child and their parent/guardian)

Project title \_\_\_\_\_

Child (or if unable, parent on their behalf) /young person to circle all they agree with:

Have you read (or had read to you) about this project? Yes/No

Has somebody else explained this project to you? Yes/No

Do you understand what this project is about? Yes/No

Have you asked all the questions you want? Yes/No

Have you had your questions answered in a way you understand? Yes/No

Do you understand it's OK to stop taking part at any time? Yes/No

Are you happy to take part? Yes/No

If any answers are 'no' or you don't want to take part, don't sign your name!

If you do want to take part, you can write your name below

Your name \_\_\_\_\_

Date \_\_\_\_\_

The doctor who explained this project to you needs to sign too:

Print Name \_\_\_\_\_

Sign \_\_\_\_\_

Date \_\_\_\_\_

Thank you for your help.

### **3.5 Information sheets for parents/guardians**

These should be designed using the guidance for information sheets for competent adults given earlier but modified appropriately.

If the child is not deemed competent to consent or the trial falls under the European Clinical Trials Directive, they need to sign a consent form after reading this information sheet and once they are happy with the explanation given. This should be separate from the children's consent or assent form.

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## **ANNEX A**

### **PUBLIC PERCEPTION OF RESEARCH**

#### **What do public or patients think of medical research?**

##### **1. Summary**

Surveys indicate that the public places high priority on medical research and wishes it to continue. If we look at why some deny consent to give us a further view it is apparent that even these people are not hostile to research and that refusal can usually be attributed to more mundane, practical, reasons.

##### **2. Evidence**

###### ***For public support***

Woolley, M. Propst, S. (2005). Public attitudes and perceptions about health care research. *The Journal of the American Medical Association*. **294**: 1380 - 1384.

The authors analysed results from surveys of public opinion in the USA. They found that 'Americans rate research as a high national priority, and they strongly support greater investment by public and private funders' although it came behind homeland security, medicare and education.

Comis, R.L. Miller, J.D. Aldigé, C.R. Krebs, L. Stoval, E. (2003). Public Attitudes Toward Participation in Cancer Clinical Trials. *Journal of Clinical Oncology*. **21**: 830 – 835.

A national sample of 1,000 adults aged 18 and older were interviewed. From this the authors extrapolated data to suggest approximately 32% of American adults (64 million individuals) would be very willing to participate in a cancer clinical trial if asked to do so. An additional 38% of adults (76 million individuals) would be inclined to participate in a cancer clinical trial but had questions. They concluded that the primary problem with accrual is not the attitudes of patients.

Harris Interactive. (2006). Public Awareness of Clinical Trials Increases: New Survey Suggests Those Conducting Trials Are Doing A Better Job of Informing Potential Participants of Opportunities. Last accessed at: <http://www.harrisinteractive.com/news/allnewsbydate.asp?NewsID=812>

Very large majorities of the public (89%) believe that clinical trials make a contribution to science.

Koops, L. Lindley, R.I. (2002). Thrombolysis for acute ischaemic stroke: consumer involvement in design of new randomised controlled. *British Medical Journal*. **325**: 415 – 417.

Consumers generally supported a planned trial, and their involvement helped to refine trial consent procedures and led to an ethically acceptable trial design. Consumer involvement can be a very important part of the development of new randomised controlled trials.

### ***Reasons for refusal***

Iversen, A. Liddell, K. Fear, N. Hotopf, M. Wessely, S. (2006). [Consent, Confidentiality, and the Data Protection Act](#) . *British Medical Journal*. **332**: 165 - 169.

In the military group studied, refusal to participate in epidemiological research was usually due to mundane issues rather than a genuine refusal to participate. 'Non response is therefore more likely to be due to factors such as time constraints...or lack of interest than distress' and in support they have found that, once contacted, few refused further access.

Tyrer, P. Seivewright, H. Ferguson, B. Johnson, T. (2003). Cold calling in psychiatric follow up: is it justified? *Journal of Medical Ethics*. **29**: 238 – 242.

This study addressed the question:

'Is non response to invitation to participate in a study passive refusal OR an expression of 'no opinion' in which case it would be fair to make further contact?'

Eighty-four of 192 patients who had participated in a trial of treatment of neurotic disorders did not respond to a follow up invitation 12 years after a study.

In this highly vulnerable group, when further contact was made of those who did not reply, 58 (69%) were positive, 16 neutral and 10 (12%) negative.

Crombie, I.K. Irvine, L. Williams, B. McGinnis, A.R. Slane, P.W. Alder, E.M. McMurdo, M.E.T. (2004). Why older people do not participate in leisure time physical activity: a survey of activity levels, beliefs and deterrents. *Age Ageing*. **33**: 287 - 292.

887 people aged 65–84 years were invited by a letter from their GP to participate in a home interview study. Overall 54% refused, most (384) by returning the postcard, the remainder (91) refused when visited or telephoned. Ethical permission was obtained to investigate the reasons for refusal to participate. After GPs excluded patients deemed ineligible, 417 people were sent an eight item questionnaire. 60% of those who initially refused to participate in the survey returned a questionnaire giving reasons for not taking part. The commonest reason (given by 56%) was that participants thought that they did not do enough activities to be of interest to the study. The other main concern was being visited at home by a research nurse (45%). The authors conclude, ‘the high response rate among those who initially refused indicates a willingness to participate in research. The finding that many of those who refused did so because they thought they were not sufficiently interesting, suggests that it was misperception rather than antipathy to the study which prompted refusal, not interested in research.’

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## **ANNEX B**

### **CONSENT**

#### **1. Summary**

Research evidence indicates that the public value their right to choose if they wish to participate in research, indicated by giving consent. Trial participants have indicated that they would be unhappy to forego this, even if the study was approved by RECs.

However, some believe that the consent process can give rise to problems. They provide evidence that it can introduce bias and that it may limit recruitment. These concerns have particular relevance in epidemiological research where an adequate and representative sample is necessary for any conclusions to have validity.

An inflexible need for consent in emergency research is problematic and it also raises problems for research involving those who may not have capacity. These topics are considered in more detail in later sections.

When recruiting participants to a clinical trial, it can be difficult to decide how much information the patient needs to provide valid consent. Guidelines state that each 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 along with appropriate action in such circumstances and possible redress. Subjects must also be made aware of their right to abstain from participation in the study or to withdraw consent to participate at any time without reprisal.

For Clinical Trials of Investigational Medicinal Products the ICH GCP 'Elements of Informed Consent' should be consulted.

## 2. Evidence

Simes, R.J. Tattersall, M.H.N. Coates, A.S. Raghaven, D. Solomon, H.J. Smartt, H. (1986). Randomised comparison of procedures for obtaining informed consent in clinical trials of treatment of cancer. *British Medical Journal*. **293**: 1065 - 1068.

Fifty-seven cancer patients were randomly allocated to total disclosure or individual approach at physicians discretion. It is puzzling that while 98% wanted to be involved, 85% wanted the doctor to make the decision.

Stenson, B.J. Becher, J.C. McIntosh, N. (2004). Neonatal research - the parental Perspective. *Archives of Disease in Childhood*. **89**: F321 - F324.

83% of 154 parents asked retrospectively would be unhappy to forego consent to recruit their baby into a trial even if approved by a REC.

Allmark, P. Mason, S. (2006). Improving the quality of consent to randomised controlled trials by using continuous consent and clinician training in the consent process. *Journal of Medical Ethics*. **32**: 439 - 443.

The vast majority (96%) of 30 interviewees felt it right they were asked for consent.

Wendler, D. Emanuel, E. (2002). The debate over research on stored biological samples: what do sources think? *Archives of Internal Medicine*. **162**: 1457 – 1462.

Data were gathered using a telephone survey of 504 individuals living in the United States. Two cohorts were studied: (1) individuals who had participated in clinical research and contributed biological samples and (2) randomly selected Medicare recipients. Of the respondents, 65.8% would require their consent for research on clinically derived, personally identified samples.

## 3. Guidance

World Medical Association Declaration of Helsinki, as amended by the 52<sup>nd</sup> WMA General Assembly, Edinburgh, Scotland, October 2000. Paragraphs 22 and 23.

In any research on human beings, 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. The subject should be informed of the right to abstain from participation in the study or to withdraw consent to participate at any time without reprisal. After ensuring that the subject has understood the information, the physician should then obtain the subject's freely-given informed consent, preferably in writing. If the consent cannot be obtained in writing, the non-written consent must be formally documented and witnessed.

When obtaining informed consent for the research project the physician should be particularly cautious if the subject is in a dependent relationship with the physician or may consent under duress. In that case the informed consent should be obtained by a well-informed physician who is not engaged in the investigation and who is completely independent of this relationship.

Department of Health (2001). Good Practice in Consent Implementation Guide: Consent to Examination and Treatment. DoH Publications, London. Last accessed at: <http://www.dh.gov.uk/assetRoot/04/01/90/61/04019061.pdf>

'Twelve key points on consent: the law in England' (Relating to treatment but has relevance to research as well).

### **When do health professionals need consent from patients?**

1. Before you examine, treat or care for competent adult patients you must obtain their consent.
2. Adults are always assumed to be competent unless demonstrated otherwise. If you have doubts about their competence, the question to ask is: 'can this patient understand and weigh up the information needed to make this decision?' Unexpected decisions do not prove the patient is incompetent, but may indicate a need for further information or explanation.
3. Patients may be competent to make some health care decisions, even if they are not competent to make others.
4. Giving and obtaining consent is usually a process, not a one-off event. Patients can change their minds and withdraw consent at any time. If there is any doubt,

you should always check that the patient still consents to your caring for or treating them.

### **Can children give consent for themselves?**

5. Before examining, treating or caring for a child, you must also seek consent. Young people aged 16 and 17 are presumed to have the competence to give consent for themselves. Younger children who understand fully what is involved in the proposed procedure can also give consent (although their parents will ideally be involved). In other cases, some-one with parental responsibility must give consent on the child's behalf, unless they cannot be reached in an emergency. If a competent child consents to treatment, a parent cannot override that consent. Legally, a parent can consent if a competent child refuses, but it is likely that taking such a serious step will be rare.

### **Who is the right person to seek consent?**

6. It is always best for the person actually treating the patient to seek the patient's consent. However, you may seek consent on behalf of colleagues if you are capable of performing the procedure in question, or if you have been specially trained to seek consent for that procedure.

### **What information should be provided?**

7. Patients need sufficient information before they can decide whether to give their consent: for example information about the benefits and risks of the proposed treatment, and alternative treatments. If the patient is not offered as much information as they reasonably need to make their decision, and in a form they can understand, their consent may not be valid.
8. Consent must be given voluntarily: not under any form of duress or undue influence from health professionals, family or friends.

### **Does it matter how the patient gives consent?**

9. No: consent can be written, oral or non-verbal. A signature on a consent form does not itself prove the consent is valid – the point of the form is to record the patient's decision, and also increasingly the discussions that have taken place.

Your Trust or organisation may have a policy setting out when you need to obtain written consent.

### ***Refusal of treatment***

10. Competent adult patients are entitled to refuse treatment, even when it would clearly benefit their health. The only exception to this rule is where the treatment is for a mental disorder and the patient is detained under the Mental Health Act 1983. A competent pregnant woman may refuse any treatment, even if this would be detrimental to the fetus.

### ***Adults who are not competent to give consent***

11. No-one can give consent on behalf of an incompetent adult. (*Note*, the law in Scotland is different and it is changing in England and Wales when the Mental Capacity Act comes into force April 2007). However, you may still treat such a patient if the treatment would be in their best interests. 'Best interests' go wider than best medical interests, to include factors such as the wishes and beliefs of the patient when competent, their current wishes, their general wellbeing and their spiritual and religious welfare. People close to the patient may be able to give you information on some of these factors. Where the patient has never been competent, relatives, carers and friends may be best placed to advise on the patient's needs and preferences.
12. If an incompetent patient has clearly indicated in the past, while competent, that they would refuse treatment in certain circumstances (an 'advance refusal'), and those circumstances arise, you must abide by that refusal.

General Medical Council (1998). Seeking Patients' consent: the ethical considerations. Consent to research (Paragraphs 36 and 37): Last accessed at: <http://www.gmc-uk.org/guidance/current/library/consent.asp#research>

You must take particular care to be sure that anyone you ask to consider taking part in research is given the fullest possible information, presented in terms and a form that they can understand. This must include any information about possible benefits and risks; evidence that a research ethics committee has given approval; and advice that they can withdraw at any time. You should ensure that participants have the opportunity to read and consider the research information leaflet. You must allow them

sufficient time to reflect on the implications of participating in the study. You must not put pressure on anyone to take part in research. You must obtain the person's consent in writing. Before starting any research you must always obtain approval from a properly constituted research ethics committee.

You should seek further advice where your research will involve adults who are not able to make decisions for themselves, or children. You should be aware that in these cases the legal position is complex or unclear, and there is currently no general consensus on how to balance the possible risks and benefits to such vulnerable individuals against the public interest in conducting research.

The principles of International Commission on Harmonisation – Good Clinical Practice (ICH GCP) guide trials of investigational medicinal products.

'Freely given informed consent should be obtained from every subject prior to clinical trial participation.'

This is defined as,

'A subject voluntarily confirms his or her willingness to participate in a particular trial, after having been informed of all aspects of the trial that are relevant to the subject's decision to participate. Informed consent is documented by means of a written, signed and dated informed consent form.'

Consent can be taken by the 'Investigator or person designated'.

The ICH GCP elements of Informed Consent are:

The information for participants should include:

- the study title and an invitation to participate;
- the trial involves research;
- the purpose of the study;
- why the participant has been chosen;
- the voluntary nature of participation and participants may withdraw from the trial at any time without penalty or loss of benefits to which they were otherwise entitled;

- the trial treatment(s) and the probability for random assignment to each treatment;
- the trial procedures to be followed, including all invasive procedures;
- those aspects of the trial that are experimental;
- the alternative procedure(s) or course(s) of treatment that may be available to the subject, and their important potential benefits and risks;
- the approximate number of participants involved in the trial;
- the participants responsibilities in the study, including the expected duration of their participation in the trial;
- the reasonably foreseeable risks or inconveniences to the subject, including specific risks on ionising radiation or pregnancy during the trial;
- the reasonably expected benefits. When there is no intended clinical benefit to the participant, they should be made aware of this;
- the subject or the subject's legally acceptable representative will be formed in a timely manner if information becomes available that may be relevant to the subject's willingness to continue participation in the trial;
- the foreseeable circumstances and/or reasons under which the subject's participation in the trial may be terminated;
- care after the trial has stopped;
- the compensation and/or treatment available to the subject in the event of trial related injury;
- 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;
- details of anticipated prorated payments and expenses, if any, for participating in the trial and any other arrangements for payment, including an explanation of how payment may be influenced by duration of participation or completion of diaries, etc.;
- assurance 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;
- what participants should do if they have a problem or a complaint regarding the trial;
- contact details are clearly stated.

Hewlett, S. (1996). Consent to clinical research--adequately voluntary or substantially influenced. *Journal of Medical Ethics*. **22**: 232 – 237.

Some guidance on how to obtain fair consent for clinical trials with a useful patient's guide at the back.

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## CONSENT FOR EPIDEMIOLOGICAL RESEARCH

### 1. Summary

Currently, obtaining consent is the default position for all research, although advice suggests that consent from individuals to use medical data is not an absolute legal requirement under the Data Protection Act (1998). Researchers present evidence which suggests that the consent process may introduce bias into the research population, that it is often impractical and that it unnecessarily limits recruitment. As epidemiological research is considered to be minimally invasive, and the potential benefit to society is significant, there is support from researchers (and the majority of public consulted) that consent could be waived when the effort and cost of doing so is disproportionate to the research being conducted. It seems that the problem is deciding when it is appropriate to (conduct research without consent).

### 2. Evidence

#### ***Researchers views on consent limiting recruitment, its occasional impracticality and introduction of bias***

Walley, T. (2006). Overzealous interpretation of UK laws is stifling epidemiological research. *British Medical Journal*. 332: 130 – 131.

The author argues that recent growth in the regulation of research has caused delays, higher costs, and sometimes cessation of research. Rules have become particularly complex and confusing. This is taken further.

'The information commissioner - an independent official appointed by the Crown to oversee the Data Protection Act 1998, the Freedom of Information Act 2000, and the Environmental Information Regulations 2004 - takes a more liberal view. The commissioner has decided that, while obtaining consent for medical research involving identifiable personal health data is the default position, consent is not required where such access to the data is necessary (for example in a research protocol approved by an ethics committee), is considered proportionate and no more with respect to privacy and public interest, and where there is 'fair processing' (meaning that the patient should be informed of the data collection and have the right to opt out). Even informing the patient may be waived if the effort to do so is disproportionate, especially if the research is 'historical or statistical' Transparency and proportionality are also

emphasised in the NHS research governance framework. Many data controllers responsible for the implementation of the Data Protection Act seem unaware that there are reasonable exceptions to the general rule of consent.'

Wanless, D. (2004). Securing Good Health for the whole population. Final report. Last accessed at: [http://www.hm-treasury.gov.uk/consultations\\_and\\_legislation/wanless/consult\\_wanless04\\_final.cfm](http://www.hm-treasury.gov.uk/consultations_and_legislation/wanless/consult_wanless04_final.cfm)

The Wanless' report (2004) seems to recognise that individual rights must be balanced against the benefit to society that research brings:

'9.16: The White Paper should address the possible threat to public health research, which arises from the difficulty of obtaining access to data because of the need to strike a balance between individual confidentiality and public health research requirements.'

Ingelfinger, J.R. Drazen, J.M. (2004). Registry research and medical privacy. *The New England Journal of Medicine*. **350**: 1452 - 1453.

Armstrong, D. Kline-Rogers, E. Jani, S.M. Goldman, E.B. Fang, J. Mukherjee, D. Nallamothu, B.K. Eagle, K.A. (2005). Potential Impact of the HIPAA privacy rule on data collection in a registry of patients with acute coronary syndrome. *Archives of Internal Medicine*. **165**: 1125-1129.

Data entry into Registries in the USA has fallen since the introduction of the Health Insurance Portability and Accountability Act.

Busby, A. Ritvanen, A. Dolk, H. Armstrong, N. De Walle, H. Riano-Galan, I. Gatt, M. McDonnell, R. Nelen, V. Stone, D. (2005). Survey of Informed Consent for Registration of Congenital Anomalies in Europe. *British Medical Journal*. **331**: 140 - 141.

A survey of such registries s demonstrated falling recruitment when opt in consent was demanded.

de Vet, H. Dekker, J.M. Van Veen, E.B. Olsen, J. (2003). -Access to data from European registries for epidemiological research. *International Journal of Epidemiology*. **32**:1114 - 1115.

Tu, J.V. Willison, D.J. Silver, F.L. Fang, J. Richards, J.A. Laupacis, A. Kapral, M.K. (2004). Impracticality of informed consent in the registry of the Canadian Stroke network. *The New England Journal of Medicine*. **350**: 1414 – 1421.

### ***The introduction of bias***

Jousilahti, P. Salomaa, V. Kuulasmaa, K. Niemela, M. Vartiainen, E. (2005). Total and cause specific mortality among participants and non-participants of population based health surveys: a comprehensive follow up of 54 372 Finnish men and women. *Journal of Epidemiology and Community Health*. **59**: 310 – 315.

'Bias and it matters'. In a large Finnish survey, mortality was higher in non - participants than participants, the largest differences being in violence and alcohol related deaths.

Dennis, M. (1997). Commentary: why we didn't ask for consent. *British Medical Journal*. **314**: 1077.

In a report of a study evaluating intervention of a stroke nurse, reasons for not consenting were presented:

- Study design would have been severely compromised (introduction of bias);
- Harm was not expected;
- Subjects could refuse to see stroke worker/psychologist if wished.

Al-Shahi, R. Vousden, C. Warlow, C. (2005). Bias from requiring explicit consent. *British Medical Journal*. **331**: 942.

In a study of adults with a brain vascular abnormality the authors found differences between adults who consent to participate in observational records-based research and those who do not, or cannot. They comment, 'blanket requirements for explicit consent for the use of individuals' identifiable data can bias disease registers, epidemiological studies, and health services research.'

Mant, J. Winner, S. Carter, J. D.T. Wade. (1997). Patient's knowledge that they are participating in trial may not bias results *British Medical Journal*. **315**: 247.

In a preliminary report of a similar study to Dennis *et al* (1997), the authors argue that bias may not be evident even if consent is sought with the full knowledge of the participant that they may be in a 'placebo' group.

Tu, J.V. Willison, D.J. Silver, F.L. Fang, J. Richards, J.A. Laupacis, A. Kapral, M.K. (2004). Impracticality of informed consent in the registry of the Canadian Stroke network. *The New England Journal of Medicine*. **350**: 1414 – 1421.

These workers found that despite employing neurology research nurses, the need for consent drastically reduced recruitment and introduced bias.

McKinney, P.A. Jones, S. Parslow, R. Davey, N. Darowski, M. Chaudhry, B. Stack, C. Parry, G. Draper, E.S. (2005). A feasibility study of signed consent for the collection of patient identifiable information for a national paediatric clinical audit database. *British Medical Journal*. **330**: 877 – 879.

Insisting on consent introduced bias in this data collection.

### ***Public opinion on consent in epidemiologic research***

Barrett, G. Cassell, J.A. Peacock, J.L. Coleman, M.P. (2006). National survey of British public's views on use of identifiable medical data by the National Cancer Registry. *British Medical Journal*. **332**: 1068 – 1072.

The authors sought to describe the views of the British public on the use of personal medical data by the National Cancer Registry without individual consent using a national cross sectional, face to face interview survey. 72% of all respondents did not consider inclusion of postcode, inclusion of name and address, and the receipt of a letter inviting them to a research study on the basis of inclusion in the registry to be an invasion of their privacy. 81% of all respondents said that they would support a law making cancer registration statutory. They concluded that most of the British public considers the confidential use of personal, identifiable patient information by the National Cancer Registry for the purposes of public health research and surveillance not to be an invasion of privacy.

Willison, D.J. Keshavjee, K. Nair, K. Goldsmith, C. Holbrook, A.M. (2003). Patients' consent preferences for research uses of information in electronic medical records. *British Medical Journal*. **326**: 373.

In a Canadian survey of 123 families broad support for research use of data was found. 74% wished to be consulted and 26% accepted 'passive' use of their data.

Whiteman, D.C. Clutton, C. Hill, D. (2006). Australian public's views on privacy and health research. *British Medical Journal*. **332**: 1274.

In a random telephone survey of 301, 192 (64%) were in favour of health databases being used for research purposes and the researchers concluded that 'most respondents were not sufficiently concerned by privacy to prevent research activities.'

Robling, M.R. Hood, K. Houston, H. Hill, R. Fay, J. Evans, H.M (2004). Public attitudes towards the use of primary care patient record data in medical research without consent: a qualitative study. *Journal of Medical Ethics*. **30**: 104 – 109.

These workers, involving 49 members of the public and four lay representatives in focus groups found a cautious attitude to research using data without consent. The lay representatives were even more cautious (in line with other work that those in a regulatory role will tend to a more conservative attitude (Nurock, 2005)). The authors acknowledge such opinion could not be considered representative and add the caveat at the end of their article that quantitative work is required to determine how widely held these views are.

Peto, J. Fletcher, O. Gilham, C. (2004). Data protection, informed consent, and research. *British Medical Journal*. **328**: 1029 – 1030.

At a public meeting in November 2002, the audience were provided with an electronic voting facility. After a discussion of the restrictions on access to medical records that British epidemiologists now face and their effects on their work, the audience were invited to vote for or against the following proposed law: 'Consent is not required for access to medical records for non-commercial medical research that has no effect on the individuals being studied and has been approved by an accredited research ethics committee.' The vote in favour was 93%. The audience included members of the

general public, patients' support groups and cancer charities, doctors, nurses, and public health workers.

Iversen, A.Liddell, K. Fear, N. Hotopf, M. Wessely, S. (2006). Consent confidentiality and the Data Protection Act. *British Medical Journal*. 332: 165 - 169.

The authors looked at their previous data to determine the perception of their past participants to approach and use of data. Refusal varied between 0.06% and 11.3%, with telephone interviews the most difficult. Postal surveys had very low stated refusal rates. They conclude, 'we are not arguing that epidemiological research should always proceed without consent. But it should be allowed to do so when the privacy interference is proportionate' and that there is 'a propensity to over predict participants distress.'

## 2. Guidance

The Canadian Institutes of Health Research 'determinants of impracticability for obtaining consent for research' highlight some of the main considerations and might be a good starting point and reference:

- size of population being researched;
- difficulty of contact either indirectly or directly;
- resultant risk of introducing bias;
- risk of breaching privacy or inflicting psychological social or other harm by contact;
- undue hardship imposed on the organisation when additional financial, material, human or other resources are required.

American Association for Public Opinion Research. (2005). Protection of human Participants in Survey Research: A source document for institutional review boards. Last accessed at: <http://infohost.nmt.edu/~red/IRB/AAPORdoc.pdf>.

Federal regulations (CFR 46.117c) on human subjects protections recognize that written consent forms are not necessary or desirable in every research setting. The regulations provide that, while written consent is the norm in much research involving humans, IRBs may waive requirements for signed consent if they find that the research

presents no more than minimal risk of harm to subjects and involves no procedures for which written consent is normally required outside of the research context.

### ***The Legal Position within the United Kingdom***

Definitive legal guidance requires expert opinion. This is an institutional responsibility but below are some recent articles discussing the legal position in the UK.

Lord Falconer of Thoroton (2000). Freedom of information bill (Hansard). Column 261 - 5.

The 1998 Data Protection Act allows medical data to be used for any medical research purpose without the need for the consent of individuals. It is not necessary to define the term 'medical research,' nor to make specific provision for it to include the monitoring of public health, which for these purposes is regarded as medical research. It is clear that many practitioners are confused between the requirements of the Data Protection Act and those of the various regulatory and representative bodies within the sector.

Information Commissioner. (2002). Use and disclosure of health data: guidance on the application of the Data Protection Act 1998.

...It is a common misconception, for instance, that the act always requires consent of data subjects to the processing of their data.

Boyd, P. (2003). Health research and the Data Protection Act 1998. *Journal of Health Services Research and Policy*. 8(sup 1): S1 - S7.

The two most widely held misconceptions are that the act creates an overarching requirement to obtain explicit consent for the processing of all health data and that the requirements of the act are additional to good professional standards, medical ethics and confidentiality. In fact, in most cases the act will almost never require consent for the processing of data for research purposes, unless consent is also a more general legal requirement.

### ***The Legal Position Outside the UK***

Forman, D. Brewster, D. (2006). Protecting the work of UK Cancer Registries. *British Medical Journal*. [Rapid response].20 May 2006. Last accessed at:  
<http://bmj.bmjournals.com/cgi/eletters/332/7549/1068>

‘Several countries, including the USA, New Zealand and Sweden, have primary legislation to ensure 100% registration’ (in Cancer Registries).

## CONSENT IN EMERGENCY RESEARCH

### 1. Summary

There are obvious difficulties in obtaining consent in emergencies; researchers have suggested, and the evidence supports the contention that patients with acute medical conditions may sometimes lack the capacity to consent and that they have inadequate time to understand all relevant information. Making choices about medical treatment can be difficult for patients and parents considering the distress of the situation.

Ethical and legal considerations may differ. Ethical considerations might propose:

#### Community consultation

Prior to a study, researchers could approach patients in a similar environment (accident and emergency departments) and ask them to comment on the proposed means of obtaining consent. Baren *et al* (1999) have described such a process (see below).

#### Prospective informed consent (PIC) before an emergency event

This may be possible but presents problems.

#### Consultation of patient groups

Researchers could determine the opinion of patient groups, who, if supportive, could spread knowledge of the trial to members.

#### Information sheets for the family

It is important that relatives are consulted **but** their exact role must be defined and the difficulties they are in.

#### Deferred consent and consent to continue

Once the patient has recovered, consent could be sought to continue the study and incorporate the patient's record into the study.

### 2. Evidence

#### ***Practical concerns with the consent process in emergency situations***

Stobbart, L. Murtagh, M.J. Louw, S.J. Ford, G.A. Rodgers, H. (2006). Consent for research in hyperacute stroke. *British Medical Journal*. **332**: 1405 – 1406.

The authors argue that essential studies in the first six hours are hampered by rules on consent.

Demarquay, G. Derex, L. Nighoghossian, N. Adeleine, P. Philippeau, F. Honnorat, J. Trouillas, P. (2005). Ethical Issues of Informed Consent in Acute Stroke. *Cerebrovascular Disease*. **19**: 65 – 68.

In this study the researchers found that only 23 of 56 patients with stroke were able to provide consent.

Roberts, I. (2003). Research in emergency situations: with or without relative's consent. *Emergency Medicine Journal*. **21**: 703.

Some hospital RECs insisted on consent, some did not. Waiving consent reduced time to randomisation (and presumably treatment).

Smithline, H.A. Mader, T.J. Crenshaw. B.J.(1999). Do patients with acute medical conditions have the capacity to give informed consent for emergency medicine research? *Academic Emergency Medicine*. **6**: 776 – 780.

Of 25 patients with acute myocardial infarction five (20%) had abnormal scores of less than five on the WAIS-R (an assessment of cognitive ability), indicating their consent would not be regarded as informed.

Elbourne, D. Snowdon, C. Garcia, J. (1997). Subjects may not understand concept of clinical trials. *British Medical Journal*. **315**: 247.

This group studied 21 families of newborn babies recruited to extracorporeal membrane oxygenation (ECMO). Difficulties for parents included randomisation and the meaning of 'a trial.' This paper outlines parents' misconceptions and proposes three hypotheses:

1. Parents given accurate information but didn't retain it.
2. Parents given partial information to soften the blow.

3. Parents given inaccurate information, which reflected caregivers understanding.

***Methods proposed by researchers to overcome difficulties with consent***

Baren, J.M. Anicetti, J.P. Ledesma, S. Biros, M.H. Mahabee-Gittens, M. Lewis, R.J. (1999). An approach to community consultation prior to initiating an emergency research study incorporating a waiver of informed consent.. *Academic Emergency Medicine*. **6**: 1210 – 1215.

Prior to study of phenytoin in acute head injured children, researchers consulted 227 parents of children attending ER for minor injuries, to ask whether they would have consented to this study if asked. 66% (149) consented, 85% of those consenting perceived personal benefit for their child, 72% perceived benefit for other children 60% furthering knowledge. Of non-consenting (78) 27% wanted to talk to other family members and 26% could not consent unless in the actual situation. This showed it was a viable method of prior consultation. Overall 18% refused.

Morley, C. (1997). Consent is not always practical in emergency treatments. *British Medical Journal*. **314**: 1480.

The author discusses four possible actions to research the condition of meconium aspiration, an emergency in neonatal care that requires further research to define best treatment.

1. Inform all antenatal women.
2. Enrol babies where consent can be obtained.
3. Study and recruit even if consent not obtained after presentation to REC.
4. Perform no trial; use current unproven treatment.

Abramson, N.S. Meisel, A. Safar, P. (1986). Deferred consent: a new approach for resuscitation research on comatose patients. *Journal of the American Medical Association*. **255**: 2466 - 2471.

Once the patient has recovered, consent could be sought to continue the study and incorporate the patient's record into the study.

Allmark, P. Mason, S. (2006). Improving the quality of consent to randomised trials using continuous consent and clinician training. *Journal of Medical Ethics*. 32: 439 – 443.

The authors describe the results of a study looking into the extremely difficult process of obtaining consent from parents whose babies have suffered birth asphyxia. They propose the term 'continuous consent' in which information is given over a period of time as it was recognised that parents would find it very difficult to give informed consent for this study. They argue that the process provides for valid informed consent.

- Element 1: Preliminary information.
- Element 2: A more comprehensive leaflet given and consent sought.
- Element 3: Consultant meets parents within 72 hours to ensure they understand the study and wish to continue.

The authors felt that training was an important part of the success of the consent process when compared to previous neonatal studies. 96% of the parents wanted to be consulted about the trial. Only two out of 30 had difficulty with the continuous consent process, both related to receiving more information at a later stage.

### **3. Guidance**

For legal considerations, expert advice should be sought.

#### ***EU Clinical trials directive***

Research involving 'investigational medicinal products (medicines)' requires the consent of the patient or representative. Up until end 2006 it did not allow waiver on this although this has changed recently in the UK.

#### ***Mental Capacity Act (England and Wales)*** (Coming into force April 2007).

Research without consultation must only take place in exceptional emergency circumstances and with well-documented reasons. Where the research requires action as part of emergency treatment, where there may not be time to consult a third party, alternative arrangements must be made and documented, such as consultation with an

identified member of staff who is independent of the research. It is the responsibility of the Principal Research Investigator to state the reasons why exemption from Third Party approval is, in his/her view, justified.

Two separate situations must be identified. The first is any emergency situation where consultation with a third party has been considered and attempted but rejected as impracticable and therefore the agreement of a medical practitioner unconnected to the research needs to be sought. The second is where the urgency of the situation is such that even this safeguard is not practicable and a procedure agreed with the Committee is followed with no consultation. RECs should consider very carefully whether any research proposal should need to carry out research without any of the above safeguards, such as a second doctor's agreement, and RECs need to document clearly the reasons for any such agreements. The Committee may wish to seek an independent second opinion on such matters. Once the patient has recovered, consent could be sought to continue the study and incorporate the patient's record into the study.

Scotland has its own legislation, [Adults with Incapacity \(Scotland\) Act 2000](#).

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## ANNEX C

### PEOPLE MAY NOT UNDERSTAND TRIALS

#### Do potential participants understand what they're told?

##### 1. Summary

The evidence supports the contention that participants don't always understand what they are agreeing to. Researchers therefore need to provide clear information and the published literature can give guidance to researchers and reviewers alike.

This difficulty gives further weight to the proposition that researchers should draw up and present information sheets to the public, patients or disease support groups.

It is also important to understand that consent is more than the presentation and reading of an information sheet. It is a process in which this is but one part.

##### 2. Evidence

***Patients may not understand the purpose of consent.***

Akkad, A. Jackson, C. Kenyon, S. Dixon-Woods, M. Taub, N. Habiba, M. (2006). Patients' perceptions of written consent: questionnaire study. *British Medical Journal*. **333**: 528.

They may not understand the information provided.

Joffe, S. Cook, E.F. Cleary, P.D. Clark, J.W. Weeks, J.C. (2001) Quality of informed consent in cancer clinical trials: A cross-sectional survey. *Lancet*. **358**: 1772 – 1777.

The authors explored the use of a questionnaire (QuIC) to assess informed consent process in cancer trials. Overall understanding was good but deficiencies were identified. Few found the decision difficult, almost none reported coercion, most were satisfied and most felt they understood the trial well. It was evident that in some cases it was not understood that treatment was 'non standard', the unproven nature of the

treatment and the uncertainty of personal benefit (the therapeutic misconception). In design these require careful consideration.

Understanding is improved by:

- a structured template;
- presence of a third party such as a nurse;
- giving the potential participant time to consider;
- encouraging careful reading and allocation of time.

Kenyon, S. Dixon-Woods, M. (2004). What do they know? A content analysis of women's perceptions of trial information. *British Journal of Obstetrics and Gynaecology*. 111: 1341 - 1345.

A questionnaire was sent to 3074 research participants. 1462 participants provided written answers to a specific question on why the study was being carried out. Content analysis suggested that the information leaflet was highly valued as a source of information about the trial. There was evidence that women's interpretations of the purpose of the trial were not identical to those that the investigators intended. Of the five key points about the trial described in the information leaflet, 400 (27%) participants reported one key point, 550 (38%) two key points, 229 (16%) three key points and 23 (1.5%) four key points. None reported five key points. Poor recall were seen in 204 (14%) of responses. This study suggests that it may not be possible to demonstrate full understanding of trial purpose and design by all participants.

Elbourne, D. Snowdon, C. Garcia, J. (1997). Subjects may not understand the concept of clinical trials. *British Medical Journal*. 315: 248 - 249.

The authors studied 21 families of critically ill newborn babies recruited to Extra Corporeal Membrane Oxygenation treatment for severe breathing problems. This paper outlines parents misconceptions and proposes three hypotheses:

- parents were given accurate information but didn't retain it;
- parents were given partial information to soften the blow;
- parents were given inaccurate information, which reflected the caregivers understanding.

Harth, S.C. Thong, Y.H. (1995). Parental perceptions and attitudes about informed consent in clinical research involving children. *Social Science and Medicine*. **41**: 1647 - 1651.

In a study of 64 parents after their child had completed a trial the authors found **some** evidence of misunderstandings.

Kodish, E. Eder, M. Noll, R.B. Ruccione, K. Lange, B. Angiolillo, A. Pentz, R. Zyzanski, S. Siminoff, L.A. Drotar, D. (2004). Communication of randomization in childhood leukemia trials. *Journal of the American Medical Association*. **291**: 470 - 475.

Most children diagnosed as having leukaemia become research subjects in randomised clinical trials (RCTs), but little is known about how randomisation is explained or understood. Despite oral and written explanation, half of the parents in this study did not understand randomisation.

Levene, M. Wright, I. Griffiths, G. (1996). Is informed consent in neonatal randomised controlled trials a ritual? *Lancet*. **347**: 475.

The authors report their experience of two concurrent neonatal trials. They argue that early consent to trials (in their case a two hour maximum) does not permit informed or educated consent.

***In treatment the same problem is evident***

Byrne, D.J. Napier, A. Cuschieri, A. (1988). How informed is signed consent. *British Medical Journal*. **296**: 839 – 840.

In a study of 100 surgical patients 27 did not know which organ had been operated upon and 44 were unaware of the exact nature of the operation.

Meropol, N.J. Weinfurt, K.P. Burnett, C.B. Balshem, A. Benson, A.B. Castel, L. Corbett, S. Diefenbach, M. Gaskin, D. Li, Y. Manne, S. Marshall, J. Rowland, J.H. Slater, E. Sulmasy, D.P. Van Echo, D. Washington, S. Schulman, K.A. (2003). Perception of Patients and physicians regarding phase 1 cancer clinical trials. *Journal of Clinical Oncology*. **21**: 2589 – 2596.

The work suggests that cancer patients offered phase I trials participation have expectations that exceed their physicians, either due to inherent optimism or miscommunication.

Mason, S. Allmark, P. (2000). Obtaining informed consent to neonatal randomised controlled trials: *Lancet*. **356**: 2045 – 2051.

The researchers interviewed 200 parents of babies recruited to neonatal studies. Fifty-nine gave valid (competent, informed, able to reason, voluntary) consent, 141 had problems in one, two, three or four areas. The patient information sheet was little used. Parents *greatly* valued involvement.

### **3. Guidance**

Wager, E. Tooley, P.J.H. Emanuel, M.B. Wood, S.F. (1995). How To Do It: Get patients' consent to enter clinical trials. *British Medical Journal*. **311**: 734 - 737.

Butow, P.N. Brown, R.F. Tattersall, M.H.N. (2000). Ethics of Clinical Trials. *New England Journal of Medicine*. **342**: 978.

Consensus after a study of audio-taped consultations in which consent to recruitment was sought was that to facilitate understanding, the standard treatment should be presented first, followed by a discussion of the patients concerns and outlining the doctor's views and attitudes. Only then should a clinical trial be introduced as an option.

Albrecht, T.L. Blanchard, C. Ruckdeschel, J.C. Convert, M. Strongbow, R. (1999). Strategic physician communication and oncology clinical trials. *Yearbook of Clinical Oncology*. **17**: 3324 – 3332.

Patients were more likely to consent if the oncologist communicated in a reflective patient centred supportive and responsive manner.

Joffe, S. Cook, E.F. Cleary, P.D. Clark, J.W. Weeks, J.C. (2001). Quality of informed consent in cancer clinical trials: A cross-sectional survey. *Lancet*. **358**: 1772 – 1777.

The authors research identified that understanding can be improved by using a template, arranging for a third party professional researcher to be present, giving time to consider participation and encouraging careful reading of the information sheet.

Jack, A.L. Womack, C. (2003). Why surgical patients do not donate tissue for commercial research. *British Medical Journal*. **327**: 262.

The consent process is facilitated by face to face interviews with a trained nurse. Training is important.

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## **ANNEX D**

### **THE IMPORTANCE OF INFORMATION**

#### **Why do we emphasize providing information?**

##### **1. Summary**

Information is the most important decision aid. It is with this that potential participants can give informed consent.

Information alone, however, is not enough. Surveys indicate that those approached to participate want material on which they can make a decision, but many wish to share the decision with their health care professional. The need for trust is still evident.

Given the disagreement on how much information potential participants in research want, any researcher is faced with considerable difficulty. This can be addressed by drawing up and presenting information sheets to patients or diseases support groups and asking for their comments.

##### **2. Evidence**

O'Connor, A.M. Stacey, D. Entwistle, V. Llewellyn-Thomas, H. Rovner, D. Holmes-Rovner, M. Tait, V. Tetroe, J. Fiset, V. Barry, M. Jones, J. (2006). Decision aids for people facing health treatment or screening decisions . The Cochrane library. Last accessed at:

<http://www.mrw.interscience.wiley.com/cochrane/clsysrev/articles/CD001431/frame.html>

'Making a decision about the best option to manage health can be difficult. Getting information on the options and the possible benefits and harms in the form of decision aids may help. Decision aids, such as pamphlets and videos that describe options, are designed to help people understand the options, consider the personal importance of possible benefits and harms, and participate in decision making. The review of trials found that decision aids improve people's knowledge of the options, create realistic expectations of their benefits and harms, reduce difficulty with decision making, and increase participation in the process. They did not seem to have an effect on

satisfaction with decision-making or anxiety.' (This study looked at treatment decisions, but its conclusions have some bearing on research.)

### ***Information alone is not enough***

Kreiger, N., F. Ashbury, Cotterchio, M. Macey, J. (2001). A Qualitative Study of Subject Recruitment for Familial Cancer Research. *Annals of Epidemiology*. 11: 219-224.

The authors conducted focus groups with cancer patients and their relatives to determine their views about such research. The discussants expressed their desire that the study be endorsed by a trusted and familiar source. Benefits should be evident and clear, risks should be explicit, and interviewees would like to introduce the study to relatives.

### ***The level of information participants want is variable***

Brewin, C. Bradley, C. (1989). Patients' preferences and randomised clinical trials. *British Medical Journal*. 299: 313 - 315.

The information sheet is only **part** of a process, particularly in some types of research.

## **3. Guidance**

Questions the Medical Research Council (MRC)(UK) feel participants may wish to ask <http://www.ctu.mrc.ac.uk/TakePart.asp>.

You might find it helpful to ask the person who has asked you to take part in a trial (this might be your doctor or nurse) some questions about it. These might include:

- What is the point of the trial? How will it help people?
- Who is taking part in it?
- If the trial is testing a drug, how often must I take it, when and for how long?
- Do you know anything about the potential side effects, risks or benefits?
- How will the trial affect my daily life?
- How often will I have to visit the clinic?
- What will happen at these visits? Will I have extra tests?
- What other medication can I take when I am taking part in this trial?

- What happens if my condition gets worse?
- How long will the trial last?
- Will I be told about the results of the trial when it ends?
- Who is funding the trial?
- Will my travel expenses be paid to take part?
- Is there anything I am not allowed to do while I am taking part in the trial?
- Who can I talk to if I have any more questions?

It is helpful to write down any questions you have in advance.

Wager, E. Tooley, P.J.H. Emanuel, M.B. Wood, S.F. (1995). How to do it: get patients consent to enter clinical trials. *British Medical Journal*. 311: 734 – 737.

In all cases, doctors should develop the skills necessary to identify how much information each patient requires, but they should remember that for clinical trials there is probably a bare minimum that all patients should receive. Byrne *et al* (1988) describe patients who simply want to be treated ... so that they can leave the hospital, forget their illness, and resume growing prize marrows as far from the medical confraternity as possible, while Brewin and Bradley (1989) describe patients who 'thrive on a diet rich in detailed information about their illness.' Doctors must decide where each patient fits on this continuum.

Training can help (and RECs increasingly look at the competence of the person seeking consent).

Fallowfield, L. Jenkins, V. Farewell, V. Saul, J. Duffy, A. Eves, R. (2002). Efficacy of a Cancer Research UK communication skills training model for oncologists: a randomised controlled trial. *Lancet*. 359: 650 – 656.

There is some evidence that communication skills improved after a training course, time and experience alone can not provide this.

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## **ANNEX E**

### **INVOLVING PATIENT GROUPS**

#### **Why should I involve patients?**

##### **1. Summary**

It is good practice, may improve trial design and recruitment and retention if researchers involve patient groups (the REC is also more likely to look favourably on your project). You will indicate an ethical, patient centred approach.

##### **2. Evidence**

Koops, L. Lindley, R.I. (2002). Thrombolysis for acute ischaemic stroke: consumer involvement in design of new randomised controlled trial. *British Medical Journal*. 325: 415.

‘Obtaining informed consent for emergency stroke treatment is difficult and presents many ethical dilemmas.’ The authors demonstrate that involvement of consumers in the design of trials on stroke is valuable. Comments from the community and from carers of those who have had a stroke can enable substantial improvement of trial information leaflets. Consumers generally supported a planned trial, and their involvement helped to refine trial consent procedures and led to an ethically acceptable trial design. Consumer involvement can be a very important part of the development of new randomised controlled trials.

Mills, E.J. Singh, S. Singh, J.A. Orbinski, J.J. Warren, M. Upshur, R.E. (2005). Designing research in vulnerable populations: lessons from HIV prevention trials that stopped early. *British Medical Journal*. 331: 1403 - 1406.

This article explores the lessons to be learnt from trials stopped early. The authors recommended strategies to improve dialogue between activists, participants and researchers:

- develop dialogue through community advisory boards;

- create national ethic committees that can set clear guidelines on national practice and over rule foreign RECs and train local RECs with community membership;
- host nations should define standard care;
- before a trial the host nation should agree a definition of effectiveness and determine access and the cost of intervention in their country;
- Increase community participation;
- ensure documented follow up after the trial to monitor adverse events;
- seek help from human rights monitors if appropriate and researching vulnerable groups;
- engage with the community, patient groups, activists and politicians.

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## **ANNEX F**

### **THE PROCESS OF OBTAINING CONSENT**

#### **How should we ask people to consider participation?**

##### **1. Summary**

This process is much more than provision of an information sheet and a signature on a consent form. Researchers need training and subjects need time to ask questions and reflect.

##### **2. Evidence**

Joffe, S. Cook, E.F. Cleary, P.D. Clark, J.W. Weeks, J.C. (2001) Quality of informed consent in cancer clinical trials: A cross-sectional survey. *Lancet*. **358**: 1772 – 1777.

The authors explored the use of a questionnaire (QuIC) to assess informed consent process in cancer trials. A structured template, presence of a third party such as a nurse, giving the potential participant time to consider, encouraging careful reading and allocation of time all improved the potential participants' understanding.

Mason, S. Allmark, P. (2000). Obtaining informed consent to neonatal randomised controlled trials: *Lancet*. **356**: 2045 – 2051.

The researchers interviewed 200 parents of babies recruited to neonatal studies.

They recommended:

- researchers should receive training in obtaining consent;
- exclusive reliance on the Information Sheets should be avoided;
- explain REC review to parents, they would feel less vulnerable and more supported if they knew research had been reviewed by an REC.

Wager, E. Tooley, P.J.H. Emanuel, M.B. Wood, S.F. (1995). How To Do It: Get patients' consent to enter clinical trials. *British Medical Journal*. **311**: 734 -737.

Butow PN Brown RF Tattersall MHN (2000) Ethics of Clinical Trials *New England Journal of Medicine*. 342: 978.

The authors provide evidence of consensus after a study of audio-taped consultations in which consent to recruitment was sought. To facilitate understanding, the standard treatment should be presented first, followed by a discussion of the patients concerns and outlining the doctor's views and attitudes. Only then should a clinical trial be introduced as an option.

Albrecht, T.L. Blanchard, C. Ruckdeschel, J.C. Convert, M. Strongbow, R. (1999). Strategic physician communication and oncology clinical trials. *Yearbook of Clinical Oncology* 17: 3324.

Patients were more likely to consent if the oncologist communicated in a reflective patient centred, supportive and responsive manner.

Jack, A.L. Womack, C. (2003). Why surgical patients do not donate tissue for commercial research. *British Medical Journal*. 327: 262.

When patients have adequate information, donating surgically removed human tissue to biomedical research in the commercial sector is not a contentious issue. The consent process is facilitated by face to face interviews with a trained nurse.

Fallowfield, L. Jenkins, V. Farewell, V. Saul, J. Duffy, A. Eves, R. (2002). Efficacy of a Cancer Research UK communication skills training model for oncologists: a randomised controlled trial. *Lancet*. 359: 650 – 656.

There is some evidence that communication skills improved after a training course, time and experience alone can not provide this.

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## **ANNEX G**

### **INFORMATION SOURCES**

#### **1. Summary**

Potential participants may require two sorts of information. They may need general information about medical research or information about the specific trial they are being asked to join. These require different sources. Check material to ensure it is relevant to your work. There will obviously be similarities between websites, and it is pointless to refer potential participants to all.

#### **2. Guidance**

Useful websites with information about trials

CERES – Consumers for Ethics in Research

<http://www.ceres.org.uk/> (This site is closing in 2007).

National Electronic Library for Health

<http://www.library.nhs.uk/trials>

The National Research Register - UK database of research projects

<http://www.nrr.nhs.uk/>

INVOLVE - Promotes public involvement in the NHS.

<http://www.invo.org.uk/>

MRC Clinical Trials Unit - Advice for potential participants including lists of trials and questions that people may wish to ask researchers.

<http://www.ctu.mrc.ac.uk/TakePart.asp>

Current Controlled Trials - Information about ongoing international randomised controlled trials.

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

National Institutes of Health - USA website with useful background information on clinical trials with some details of trials in the US.

[http://clinicaltrials.gov/ct/gui/c/w1b/screen/PrintURL?file=resources.html&JServSessionIdcs\\_current=e7rhe2u5q5](http://clinicaltrials.gov/ct/gui/c/w1b/screen/PrintURL?file=resources.html&JServSessionIdcs_current=e7rhe2u5q5)

CancerHelp UK - There is a search to help people find cancer clinical trials and trial information.

<http://www.cancerhelp.org.uk>

<http://www.cancerhelp.org.uk/help/default.asp?page=51>

Cancer BACUP - Provides explanations about aspects of medical research. There is a search engine which looks through a number of databases for cancer research trials in the UK and Europe.

<http://www.cancerbackup.org.uk/Home>

<http://www.cancerbackup.org.uk/Trials/Search>

<http://www.cancerbackup.org.uk/Trials/Understandingtrials>

The National Translational Cancer Research Network - A list of trials for people with cancer that are currently recruiting patients.

[www.ntrac.org.uk](http://www.ntrac.org.uk)

National Cancer Institute - Provides information on cancer trials and how to find clinical trials.

[http://www.cancer.gov/clinical\\_trials/](http://www.cancer.gov/clinical_trials/)

The National AIDS Manual, NAM - HIV/AIDS UK trials and background information on clinical trials.

<http://www.aidsmap.com/en/main/sitemap.asp?404=true>

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## **ANNEX H**

### **RESEARCH INVOLVING CHILDREN**

#### **1. Summary**

Evidence indicates research involving children is needed, and organisations involved in child health support this view. This need is reflected both in political policy and guidance to RECs.

Guidance from expert groups is by and large in harmony.

Risk in children's research is a difficult area; guidance to answer the question 'what constitutes an acceptable risk for a child participating in a research study?' is limited and guarded. It may be this can only be decided 'case by case', using the guidance below.

#### **2. Evidence**

***It isn't a new consideration!***

Mons, G (1751 - 1752). Observations on the Effects of the Vitrum Antimonii Ceratum. *Philosophical Transactions of The Royal Society*. **47**: 273 - 278.

'Antimony mixed with yellow wax and heated over flame....I should never have ventured to give this medicine to pregnant women if chance had not convinced that it is not more dangerous... for among several women I cured of bloody fluxes there were some, that were actually with child. They were all cured and no accident happened to them. In pursuance I thought I might try it with all imaginable precautions even on sucking children. The medicine succeeds equally well in uterine evacuations.'

***There is a clear need***

Association of British Pharmaceutical Industries. Clinical trials and children's medicines. Last accessed at:

[http://www.abpi.org.uk/publications/briefings/clinical&child\\_brief.pdf](http://www.abpi.org.uk/publications/briefings/clinical&child_brief.pdf)

Much childhood prescription is either off label or unlicensed, hence the correct dose is not known and responsibility for misadventure lies with the prescriber:

- 90% in NICU;
- 45% on general paediatric wards;
- 20% in general practice.

The Association of British Pharmaceutical Industries (ABPI) argues that in the absence of formal clinical trials, all young patients given medicines that are not licensed become part of an unofficial trial with no agreed protocol, no ethics committee review, formal data capture nor efficient channels through which to disperse the information.

### **3. Guidance**

Medical Research Council (2004). MRC Ethics Guide: Medical research involving children. Last accessed at:

<http://www.mrc.ac.uk/Utilities/Documentrecord/index.htm?d=MRC002430>

While we have a responsibility to protect children, we also have an ethical obligation to ensure that they receive the best treatment. Like adults, they should be given the opportunity to benefit from the results of successful research. Medical research involving children is essential for advancing child health and well-being. Often it is not sufficient, scientific, or ethical to carry out research with adults and apply the findings to children. This may be because:

- The disease processes in children may differ from those in adults. Some childhood diseases have no close analogies in adults, therefore to understand these in any detail it is necessary to carry out research with children.
- The physiology of children is different from that of adults, and the pharmacokinetics of many drugs will vary with the age of the child. Treatments designed specifically to meet the needs of children ensure that age-related differences in drug handling and/or effects are recognised, that the doses needed for efficacy are understood, and that any adverse effects can be avoided.

- Many disorders can only be understood in the context of a child's growth and development. Examples include changes in the visual system following early squint, or the way the developing brain adapts to injury or damage in babies.
- Children are not small adults. For the therapy to be effective, its delivery must suit their needs. Use of adult formulations is often not suitable, e.g., many children find it easier to swallow a liquid formulation than a tablet. Research with children can also play a key part in increasing our understanding of some adult diseases that are thought to have their origins in early life. It enables the development of preventive intervention into the natural history of the disease. The findings of research involving children can therefore also be relevant for adults.

### ***Principles to guide research involving children***

Hull, D. (2000). Guidelines for the ethical conduct of medical research involving children Royal College of Paediatrics and Child Health. *Archives of Disease in Childhood*. 82: 181 - 182.

Its principles:

- research involving children is important for the benefit of all children and should be supported, encouraged and conducted in an ethical manner;
- children are not small adults, they have an additional unique set of interests research should only be done on children if comparable research in adults could not answer the same question;
- a research procedure which is not intended directly to benefit the child subject is not necessarily either unethical or illegal;
- all proposals should be submitted to a research ethics committee;
- legally valid consent should be obtained from the child, parent or guardian as appropriate;
- when parental consent is obtained the agreement of school age children who take part should be requested.

Research is worthwhile if it:

- has the prospect of benefit;

- is well designed and conducted;
- does not simply duplicate previous work;
- is not undertaken primarily for financial or professional advantage;
- involves a statistically appropriate number of subjects;
- is to be properly reported.

Medical Research Council (2004). MRC Ethics Guide: Medical research involving children. Last accessed at:

<http://www.mrc.ac.uk/Utilities/Documentrecord/index.htm?d=MRC002430>

Summary of key ethical principles relating to research involving children:

- Research should only include children where the relevant knowledge cannot be obtained by research in adults.
- The purpose of the research is to obtain knowledge relevant to the health, well being or healthcare needs of children.
- Researchers can only involve competent children if they have obtained their informed consent beforehand.
- A child's refusal to participate or continue in research should always be respected.
- If a child becomes upset by a procedure, researchers must accept this as a valid refusal.
- Researchers should involve parents/guardians in the decision to participate wherever possible, and in all cases where the child is not yet competent. (Exceptional circumstances where this is not possible are discussed).
- Researchers should attempt to avoid any pressures that might lead the child to volunteer for research or that might lead parents to volunteer their children, in the expectation of direct benefit (whether therapeutic or financial).
- Research involves partnership with the child and/or family, who should be kept informed and consent to separate stages of the project. Obtaining consent is a continuing process, rather than a one-off occurrence. Children and their families are likely to appreciate some recognition of their role in this partnership, such as a certificate of participation.
- Researchers must take account of the cumulative medical, emotional, social and psychological consequences of the child being involved in research. Children with certain conditions may be exposed to a sequence of research projects. It is advisable to consider the risks of a particular research procedure

in the context of the child's overall involvement in projects by different researchers.

### ***Risk and research involving children***

Royal College of Paediatric and Child Health (UK) (<http://www.rcpch.ac.uk/>)

When considering harm, rather than the lack of possible benefit, it starts with a broad, cautious statement, 'childhood is a vulnerable formative time, when harms can have serious impact. Potential harms should be assessed carefully before children are put at risk.'

Overall, it adopts a utilitarian stance and recognises that some ethical research may subject children to some harm. 'The attempt to protect children absolutely from the potential harms of research denies any of them the potential benefit.'

It defines levels of risk:

#### Minimal

Questioning, observing and measuring children, Collecting a urine sample (not by aspiration), Using 'spare' blood obtained for clinical use.

#### Low

Procedures that cause 'brief pain or tenderness.'

#### High

(Lung, liver) biopsy arterial puncture

It goes no further than the statement, 'we believe that research in which children are submitted to more than minimal risk with only slight or uncertain benefit deserves serious ethical consideration.'

### USA: Federal Regulations

These define four categories of research on children and requirements for consent:

1. Less than minimal risk -- child's assent and parent/guardians permission.
2. Greater than minimal risk but with the possibility of yielding benefit -- child's assent and parent/guardian's permission and that IRB/REC finds risk justified by anticipated benefit and the risk benefit ratios at least as favourable as the alternative approaches.

3. Greater than minimal risk but with no possibility of yielding benefit but will provide generalisable results --approval requires that the IRB/REC find the risk represents a minor increase over minimal risk and research will provide generalisable vital knowledge. This requires assent of child and permission of both parents.
4. Other than 1, 2, 3 requires consideration by secretary of HHS after consultation with expert panel.

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## **ANNEX I**

### **RANDOMISATION**

#### **1. Summary**

Randomisation is a necessary scientific method but poorly understood. Its purpose and method therefore require careful explanation.

#### **2. Evidence**

It has proved itself of value

Tobias, J.S. Informed consent and the introduction of new cancer treatments. In: Williams, C.J. (ed) (1992). Introducing new treatments for cancer: practical, ethical and legal problems. Chichester: John Wiley & Sons. 67 - 77.

'Randomisation is a blunt and brutal tool. Yet it was a randomised controlled trial that demonstrated the equal efficacy of mastectomy and breast preservation (National Surgical Adjuvant Breast Project). But can we expect patients to understand and accept that the choice between mastectomy and breast preservation has been made this way?'

Subjects **do** understand the current recommended words but there is evidence in the literature of misunderstanding of the concept.

Kerr, C. Robinson, E. Stevens, A. Braunholtz, D. Edwards, S. Lilford, R. (2004). Randomisation in trials: do potential trial participants understand it and find it acceptable. *Journal of Medical Ethics*. **30**: 80 – 84.

The authors conducted this work to examine lay persons' ability to identify methods of random allocation and the acceptability of using methods of random allocation in a clinical trial context. 130 adults attending further education colleges were recruited. The majority judged correctly that allowing people their preference was not random, and that the following were random: using a computer with no information about the individual (recommended wording for Type 3 REC trial leaflets), tossing a coin, drawing

a name out of a hat. Judgements were split over allocating people in turn (not a random allocation method but shares features with randomisation). They conclude that current UK guidelines' recommended description of random allocation by computer seems warranted. However, while potential trial participants may understand what random allocation means, they may find it unacceptable unless offered an acceptable justification for its use.

Allmark, P. Mason, S. (2006). Improving the quality of consent to randomised controlled trials by using continuous consent and clinician training in the consent process. *Journal of Medical Ethics*. 32: 439 - 443.

The authors interviewed parents whose newborn baby had suffered birth asphyxia and been recruited into a controlled trial of therapeutic cooling. They provide evidence of misunderstanding.

'Generally those who received control were disappointed, whereas those who received cooling were relieved...The main reason parents gave for their consent was the hope that trial entry would improve their baby's prospects.'

The authors felt that training was an important part of the success of the consent process when compared to previous neonatal studies.

Kodish, E. Eder, M. Noll, R.B. Ruccione, K. Lange, B. Angiolillo, A. Pentz, R. Zyzanski, S. Siminoff, L.A. Drotar, D. (2004). Communication of randomization in childhood leukemia trials. *Journal of the American Medical Association*. 291: 470 - 475.

Most children diagnosed as having leukaemia become research subjects in randomised clinical trials (RCTs), but little is known about how randomisation is explained or understood. Despite oral and written explanation, half of the parents in this study did not understand randomisation. To make informed consent more effective, future research must seek to improve communication during this critical interchange.

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## **ANNEX J**

### **PLACEBO**

#### **1. Summary**

Before a new drug can be marketed, it is necessary to prove that it is safe and effective. It is generally agreed that placebo controlled clinical trials provide the best assessment of efficacy. However, the use of placebo in trials raises ethical issues.

Careful consideration is needed prior to placebo controlled trials when standard therapy exists, but it seems the consensus is that this can be acceptable, provided certain conditions are met.

#### **2. Evidence**

##### ***The scientific value of placebo***

Hypericum Depression Trial Study Group. (2002). Effect of Hypericum perforatum (St. John's Wort) in major depressive disorder. A randomised controlled trial. *The Journal of American Medical Association*. **287**: 1807 – 1814.

Demonstrating the value of placebo.

##### ***The ethical problems of placebo.***

Emanuel, E.J. Wendler, D. Grady, C. (2000). What Makes Clinical Research Ethical? *The Journal of American Medical Association*. **283**: 2701 – 2711.

For a 'fair trial' there must be uncertainty within the scientific community about whether the new intervention is better than the comparator. Otherwise some of the subjects will receive treatment, known to be inferior. The authors present an example (a study of antiemetics). Investigators conducted a placebo-controlled trial randomising cancer patients receiving emetogenic chemotherapy to either placebo (inferior treatment) or serotonin antagonists. They argued that this placebo-controlled trial of the serotonin

antagonists for chemotherapy-induced emesis added no useful information and harmed those allocated to placebo.

Emanuel, E.J. Miller, F.G. (2001). The ethics of placebo controlled trials - A middle ground. *New England Journal of Medicine*. 345: 915 – 919.

The authors maintain they stand between what they describe as Placebo orthodoxy (placebo trials are scientifically necessary) and active-control orthodoxy (placebo controlled trials sacrifice patient interest to scientific rigor).

They argue for a middle ground:

Both sides should agree that **some** placebo trials are unethical

Advocates of active control; should agree that trials are ethical where there is only minimal chance that those allocated to placebo will suffer even minimal harm

It needs to be recognised that an equivalence trial (measuring a new medicine against current practice) needs to be larger than a placebo trial and consequently a larger number of subjects may be subjected to possible toxic effects of a new medication. In such a case a prior placebo controlled trials might be ethical.

In cases of placebo trials, ethical scrutiny must be rigorous. The magnitude of harm likely to be caused by using placebo must be part of the ethical consideration.

RECs should ensure:

- participants must understand that he or she could be on placebo;
- participants at risk of harm from non-response are excluded;
- placebo is limited to minimum period possible;
- subjects will be carefully monitored;
- researchers are ready to recognise adverse events;
- rescue intervention is available.

Temple, R. Ellenberg, S.S. (2000). Placebo-Controlled Trials and Active-Control Trials in the Evaluation of New Treatments. *Annals of Internal Medicine*. 133: 455 – 463.

This article considers the ethical concerns about use of placebo controls and describes the limited ability of active-control equivalence (also known as non-inferiority) trials to establish efficacy of new therapies in many medical contexts. The authors conclude that placebo-controlled trials are not uniformly unethical.

### ***Public perception of placebo use***

Welton, A.J. Vickers, M.R. Cooper, J.A. Meade, T.W. Marteau, T.M. (1999). Is recruitment more difficult with a placebo arm in randomised controlled trials? A quasirandomised, interview based study. *British Medical Journal*. **318**: 1114 – 1117.

Of 218 women told about a trial without a placebo arm, 85 (39%) indicated their willingness to enter compared with 65 (30%) of the 218 women told about a trial with the placebo arm ( $p = 0.06$ ). Only part of this difference was due to explicit reluctance to take a placebo. The reasons most frequently cited for not wanting to take part were reluctance to restart periods, not wanting to take unknown or unnecessary tablets, or not wanting to interfere with present good health.

## **3. Guidance**

Medical Research Council. (2004). Research Involving Human Participants in Developing Societies. Ethical Guidelines for MRC-sponsored Studies. Last accessed at: <http://www.mrc.ac.uk/Utilities/Documentrecord/index.htm?d=MRC002461>

With respect to placebo-controlled trials, the MRC follows the recommendation of the Council for International Organisations of Medical Sciences, 2002, that placebo may be used when: ‘Use of an established effective intervention as comparator would not yield scientifically reliable results and use of placebo would not add any risk of serious or irreversible harm.’

U.S. Food and Drug Administration (1998). Drug Study Designs In: Information Sheets: Guidance for Institutional Review Boards and Clinical Investigators. Last accessed at: <http://www.fda.gov/oc/ohrt/irbs/drugsbiologics.html#study>

Before a new drug or biologic can be marketed, its sponsor must show, through adequate and well-controlled clinical studies, that it is effective. FDA regulations

[21 CFR 312.126] cite five different kinds of controls that can be useful in particular circumstances:

- placebo concurrent control;
- dose-comparison concurrent control;
- no-treatment concurrent control;
- active-treatment concurrent control;
- historical control.

No general preference is expressed for any one type, but the study design chosen must be adequate to the task. Placebo control, no-treatment control (suitable where objective measurements are felt to make blinding unnecessary), and dose-comparison control studies are all study designs in which a difference is intended to be shown between the test article and some control. The alternative study design generally proposed to these kinds of studies is an active-treatment concurrent control in which a finding of no difference between the test article and the recognized effective agent (active-control) would be considered evidence of effectiveness of the new agent.

There are circumstances in which this is a fully valid design. Active-controls are usually used in antibiotic trials, for example, because it is easy to tell the difference between antibiotics that have the expected effect on specific infections and those that do not. In many cases, however, the active-control design may be simply incapable of allowing any conclusion as to whether or not the test article is having an effect.

There are three principal difficulties in interpreting active-control trials. First, active-control trials are often too small to show that a clinically meaningful difference between the two treatments, if present, could have been detected with reasonable assurance; i.e., the trials have a high 'beta-error.' In part, this can be overcome by increasing sample size, but two other problems remain even if studies are large. One problem is that there are numerous ways of conducting a study that can obscure differences between treatments, such as poor diagnostic criteria, poor methods of measurement, poor compliance, medication errors, or poor training of observers. As a general statement, carelessness of all kinds will tend to obscure differences between treatments. Where the objective of a study is to show a difference, investigators have powerful stimuli toward assuring study excellence. Active-control studies, however, which are intended to show no significant difference between treatments, do not provide the same incentives toward study excellence, and it is difficult to detect or assess the kinds of poor study quality that can arise. The other problem is that a

finding of no difference between a test article and an effective treatment may not be meaningful. Even where all the incentives toward study excellence are present, i.e., in placebo-controlled trials, effective drugs are not necessarily demonstrably effective (i.e., superior to placebo) every time they are studied. In the absence of a placebo group, a finding of no difference in an active-control study therefore can mean that both agents are effective, that neither agent was effective in that study, or that the study was simply unable to tell effective from ineffective agents.

For certain drug classes, such as analgesics, antidepressants or anti-anxiety drugs, failure to show superiority to placebo in a given study is common. This is also often seen with anti-hypertensives, anti-angina drugs, anti-heart failure treatments, antihistamines, and drugs for asthma prophylaxis. In these situations, active-control trials showing no difference between the new drug and control are of little value as primary evidence of effectiveness and the active-control design (the study design most often proposed as an alternative to use of a placebo) is not credible. In many situations, deciding whether an active-control design is likely to be a useful basis for providing data for marketing approval is a matter of judgment influenced by available evidence. If, for example, examination of prior studies of a proposed active-control reveals that the test article can very regularly (almost always) be distinguished from placebo in a particular setting (subject population, dose, and other defined parameters), an active-control design may be reasonable if it reproduces the setting in which the active-control has been regularly effective. It is often possible to design a successful placebo-controlled trial that does not cause investigator discomfort nor raise ethical issues. Treatment periods can be kept short; early 'escape' mechanisms can be built into the study so that subjects will not undergo prolonged placebo-treatment if they are not doing well. In some cases randomized placebo-controlled therapy withdrawal studies have been used to minimize exposure to placebo or unsuccessful therapy; in such studies apparent responders to a treatment in an open study are randomly assigned to continued treatment or to placebo. Subjects who fail (e.g., blood pressure rises, angina worsens) can be removed promptly, with such failure representing a study endpoint. Institutional Review Boards (IRBs) may face difficult issues in deciding on the acceptability of placebo-controlled and active-control trials. Placebo-controlled trials, regardless of any advantages in interpretation of results, are obviously not ethically acceptable where existing treatment is life-prolonging. A placebo-controlled study that exposes subjects to a documented serious risk is not acceptable, but it is critical to review the evidence that harm would result from denial of active treatment, because alternative study designs, especially active-control studies,

may not be informative, exposing subjects to risk but without being able to collect useful information.'

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## ANNEX K

### EXPENSES /PAYMENTS

#### 1. Summary

Guidance recognises payment but gives no clear indication of acceptable amounts.

In the limited literature it seems that current scales of remuneration did not blind subjects to risk.

#### 2. Evidence

It seems that current scales of remuneration did not blind subjects to risk.

Halpern, S.D. Karlawish, J.H.T. Casarett, D. Berlin, J.A. Asch, D.A. (2004). Empirical assessment of whether moderate payments are undue or unjust inducements for participation in clinical trials. *Archive of Internal Medicine* .164: 801 - 803.

The authors presented hypothetical placebo-controlled trials of a new antihypertensive drug to 126 patients with mild-to-moderate hypertension recruited from hypertension and general medicine clinics at a university hospital. Although higher payment motivated research participation, they found no evidence that commonly used payment levels represent undue or unjust inducements.

Bentley, J.P. Thacker, P.G. (2004) The influence of risk and monetary payment on the research participation decision making process. *Journal of Medical Ethics*. 30: 293 – 298.

To determine the effects of risk and payment on subjects' willingness to participate, and to examine how payment influences subjects' potential behaviours and risk evaluations, the authors studied a group of students who had enrolled at a US pharmacy school. They read a recruitment notice and informed consent form for a hypothetical study, and then completed a questionnaire. Increased monetary payments did not appear to blind respondents to the risks of a study. Payment had some influence on respondents' potential behaviours regarding concealing information

about restricted activities. 'Monetary payments appear to do what they are intended to do: make subjects more willing to participate in research. Concerns about payments blinding subjects to risks could not be substantiated in the present study.'

### 3. Guidance

International Conference on Harmonisation (1997). Harmonised Tripartite Guideline. Guidance for Good Clinical Practice E6 (R1). Last accessed at: <http://www.ich.org/LOB/media/MEDIA482.pdf>.

3.1.2 The IRB/IEC should obtain...information about payments and compensation available to subjects.

3.1.8 The IRB/IEC should review both the amount and method of payment to subjects to assure that neither presents problems of coercion or undue influence on the trial subjects. Payments to a subject should be prorated and not wholly contingent on completion of the trial by the subject.

3.1.9 The IRB/IEC should ensure that information regarding payment to subjects, including the methods, amounts, and schedule of payment to trial subjects, is set forth in the written informed consent form and any other written information to be provided to subjects. The way payment will be prorated should be specified.

4.8.10 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: the anticipated, prorated payment, if any, to the subject for participating in the trial.

Dickert, N. Grady, C. (1999). What's the price of a research subject? Approaches to payment of research participation. *New England Journal of Medicine*. 341: 198 - 203.

Although payments for participation in research have a long history, these authors felt that no consensus has been reached and even FDA advice seems contradictory. They explored, 'how much?' And suggested it should be based on:

- length of residence;
- number of visits;
- time and inconvenience;
- discomfort.g. bronchoscopy, NG tube;
- hourly rate (minimum wage?);

- **but**, never for 'risk'.

They felt it was an important issue for research ethics. Undue inducement could reduce voluntariness or understanding of the research project and what it entails. They present three payment models:

- market model - payment controlled by supply and demand;
- wage payment model - payment at unskilled work level, with extra for burdensome procedures;
- reimbursement model; payment according to the financial loss incurred by subjects.

They argue that the second seems most ethically acceptable, but there is no consensus. They felt it would seem a reasonable starting point.

<i>Table 1 Models of reimbursement in the setting of a phase 1 pharmacokinetic study involving 50 hours of the participants time.</i>			
<i>Variable</i>	<i>Market Model</i>	<i>Wage Payment Model</i>	<i>Reimbursement Model</i>
<i>Justification</i>	<i>Recruitment of subjects is vital to research and the monetary incentive will facilitate same</i>	<i>Participation in research takes time and effort and may include uncomfortable procedures</i>	<i>There should not be any financial sacrifice by the research subject</i>
<i>Function</i>	<i>Incentive</i>	<i>Compensation for time and effort</i>	<i>Reimbursement of expenses</i>
<i>Components</i>	<i>£15 per hour (for 50 hours) plus completion bonus of £200</i>	<i>£4.40 per hour (for 50 hours) (variable)</i>	<i>£20 travel expenses</i>
<i>Total payment</i>	<i>£950</i>	<i>£220</i>	<i>£20</i>

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## **ANNEX L**

### **THE CONSEQUENCES OF RESEARCH**

#### **Does research harm?**

##### **1. Summary**

Research carries a low risk of harm; however there have been rare catastrophic results. The most publicised examples of harm are from early drug work (phase I or II), but later work has risk which is difficult to identify as separation from treatment effects is problematic.

Society might forbid research. This would reduce research risk but it would maximise random disaster resulting from the use of inadequately investigated drugs or health practice. It seems very likely that more individuals would be damaged, but the damage would be random rather than confined to research subjects.

If research is to continue, and the evidence is that the public wish this ([Annex A](#)), the researcher and regulator must share the responsibility of explaining risk to potential participants.

One purpose of the information sheet is to explain clearly any possible harm. Harm is a combination of likelihood and consequence. It is clear however that we all have different levels of acceptable harm (both likelihood and consequence). This may also change according to our circumstances. Researchers therefore need to have the skills to explain risk where necessary to allow potential participants to make up their own minds and to have tested it on likely patient groups.

##### **2. Evidence**

Savulescu, J. (2002). Two deaths and two lessons: Is it time to review the structure and function of research ethics committees? *Journal of Medical Ethics*. 28: 1.

In this editorial the author explores two deaths in the USA as a result of medical experimentation. Ellen Roche, a healthy volunteer died as a result of experimental inhalation of hexamethonium. Jesse Gelsinger suffered from a mild form of an

inherited metabolic disorder which questionably didn't need treating, yet died as a consequence of experimental genetic therapy. He outlines what he feels were contributory factors.

Goodyear, M.D.E. (2006). Further lessons from the TGN1412 tragedy. *British Medical Journal*. 333: 270 – 271.

An editorial commenting on the review of a phase I trial in which six volunteers suffered life threatening complications.

### ***Evidence of variable risk acceptance***

Silvestri, G. Pritchard, R. Welch, H.G. (1998). Preferences for chemotherapy in patients with advanced non-small cell lung cancer: descriptive study based on scripted interviews. *British Medical Journal*. 317: 771 – 775.

Eighty-one patients treated with cis platinum for lung cancer were interviewed. Several accepted toxicity for survival benefits of only one week while others would not accept this even for a 24 month benefit. Half would accept mild toxicity only if it provided improved survival of four and a half months: severe toxicity would need to provide nine months increased survival. If given choice between supportive and chemotherapy only 18% chose chemotherapy for benefit of three months. Two thirds (68%) chose this if it substantially reduced symptoms even without prolonging life.

Shah, S. Whittle, A. Wilfond, B. Gensler, G. Wendler, D. (2004). How Do Institutional Review Boards Apply the Federal Risk and Benefit Standards for Paediatric Research? *The Journal of the American Medical Association*. 291: 476 – 482.

The authors conducted this study to determine how Institutional Review Board (IRB) Chairs (n -188) apply federal guidance on risk and benefit categories for paediatric research. A single blood draw was the only procedure categorized as minimal risk by a majority (152 or 81%) of the 188 respondents. An electromyogram was categorized as minimal or a minor increase over minimal risk by 100 (53%) and as more than a minor increase over minimal risk by 77 (41%). Allergy skin testing was categorized as minimal risk by 43 IRB Chairpersons (23%), a minor increase over minimal risk by 81 (43%), and more than a minor increase over minimal risk by 51 (27%). Regarding benefits, 113 chairpersons (60%) considered added psychological counselling to be a

direct benefit, while participant payment was considered a direct benefit by 10% (n = 19). They concluded that application of the federal risk and benefit categories for paediatric research was variable and sometimes contradicted by the available data on risks and the regulations themselves.

Horrobin, D.F. (2003). Are large clinical trials in rapidly lethal diseases usually unethical? *Lancet*. **361**: 695-697.

This moving article is written by a past biomedical researcher who recently developed mantle cell lymphoma, a life threatening malignancy. From his point of view he argues that most people are more interested in therapy offering the remote chance of a cure, rather than the certainty of toxicity and the near certainty of only a small response. He continues to propose that 50 years ago good scientific evidence of a potential therapeutic effect from a compound, even if only on theoretical grounds, would have quickly generated small clinical trials with little expense. These would have missed marginal but not large effects. It is the latter, he argues that people in his position want. His view of the medical world is that this is now impossible. Requirements of ethics committees, clinical trial regulations and research costing make such ventures prohibitively expensive, and as a consequence scores of compounds with potential therapeutic benefit will never be tested. This he argues is an unethical situation. The way forward is to undertake small studies, testing a wide range of compounds and looking for significant effects. The present approach of a small number of large studies capable of determining small effects is not what patients want. They wish for cure, not brief life extension, if necessary at the risk or cost of toxicity.

Nurock, S. (2005). Patients may be less risk averse than committees. *British Medical Journal*. **330**: 471 – 472.

‘Sometimes, however, it feels as though ethics committees are putting up barriers to much needed research. As a former carer for my husband, a general practitioner who developed Alzheimer's disease in his fifties, I know that some people with dementia and their carers perceive acceptable risk differently from ethics committees and are more willing to take risks, feeling there is little to lose. Indeed, research has shown that carers and people with dementia are particularly altruistic in their desire to be included in research.’

### 3. Guidance

Thomson, R. Edwards, A. Grey, J. (2005). Risk communication in the clinical consultation. *Clinical Medicine*. 5: 465 - 469.

This article seeks to summarize the state of knowledge of risk communication. Although addressing risk in the clinical context this article can give some guidance for research:

1. It is important at the outset to discern the patients' fears; no technology or language can replace an empathetic approach.
2. Recognize risk has 'likelihood' and 'consequence' which both need explanation.

Interestingly the authors provide evidence that there is little support to the idea that subjects or patients prefer risk expressed in terms of other every day (or unlikely) happenings e.g. road traffic accident, lightning strikes. They suggest, when expressing risk:

- beware of 'single event probability' – subjects can't have 5% of a stroke;
- beware relative risks;
- use single denominators where possible;
- graphical presentation can help but needs careful design - an example is presented;
- pilot test presentation of risk.

Paling, J. (2003). Strategies to help patients understand risk. *British Medical Journal*. 327: 745 – 748.

This author suggests:

- supplement words with numbers;
- use absolute numbers;
- use visual aids where possible;
- check that the patient has turned data into understanding.

Calman, K. (2002). Communication of risk: choice, consent and trust. *Lancet*. **360**: 166-168.

Explaining risk, primarily in the field of public health.

Edwards, A. Unigwe, S. Elwyn, G. Hood, K. (2003). Effects of communicating individual risks in screening programmes. *British Medical Journal*. **327**: 703 – 709.

A systematic review of studies on uptake of screening after explanation of risk.

O'Connor, A.M. Légaré, F. Stacey, D. (2003). Risk communication in practice: the contribution of decision aids. *British Medical Journal*. **327**: 736 – 740.

A discussion of decision aids in clinical practice.

Edwards, A. Elwyn, G. Gwyn, R. (1999). General practice registrar responses to the use of different risk communication tools in simulated consultations: a focus group study. *British Medical Journal*. **319**: 749 – 752.

Training helps. Their group work demonstrated that 'risk communication tools' and training helped doctors feel more comfortable and skilled in explaining risk.

Edwards, A. Elwyn, G. Mulley, A. (2002). Explaining risks: turning numerical data into meaningful pictures. *British Medical Journal*. **324**: 827 – 830.

The authors argue that patients often desire more information than is currently provided and that communicating about risks should be a two way process in which professionals and patients exchange information and opinions about those risks. Professionals need to support patients in making choices by turning raw data into information that is more helpful to the discussions than the data.

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## **ANNEX M**

### **RISKS**

#### **1. Summary**

It is clear that we all differ in our acceptance and understanding of risk. Work is needed on how to present risks and this variation reinforces the need to consider risk and discuss it where relevant with the patient group or similar bodies.

#### **2. Evidence**

Silvestri, G. Pritchard, R. Welch, H.G. (1998). Preferences for chemotherapy in patients with advanced non-small cell lung cancer: descriptive study based on scripted interviews. *British Medical Journal*. 317: 771 - 775.

Eighty-one patients treated with cis platinum for small cell lung cancer were interviewed to re-assess their preferences for treatment. Researchers found that willingness varied enormously. Several would accept toxicity for survival benefits of only one week while others would not accept this even for a 24 month benefit. Half would accept mild toxicity only if it provided improved survival of four and a half months: severe toxicity would need to provide nine months increased survival. If given choice between supportive and chemotherapy only 18% chose chemotherapy for benefit of three months. Two thirds (68%) chose this if it substantially reduced symptoms even without prolonging life.

Below is an article showing that RECs have different risk profiles.

Shah, S. Whittle, A. Wilfond, B. Gensler, G. Wendler, D. (2004). How Do Institutional Review Boards Apply the Federal Risk and Benefit Standards for Pediatric Research? *Journal of the American Medical Association*. 291: 476 – 482.

The authors conducted this study to determine how Institutional Review Board (IRB) Chairs (n -188) apply federal guidance on risk and benefit categories for paediatric research. A single blood draw was the only procedure categorized as minimal risk by a majority (n - 152 or 81%) of the 188 respondents. An electromyogram was

categorized as minimal or a minor increase over minimal risk by 100 (53%) and as more than a minor increase over minimal risk by 77 (41%). Allergy skin testing was categorized as minimal risk by 43 IRB chairpersons (23%), a minor increase over minimal risk by 81 (43%), and more than a minor increase over minimal risk by 51 (27%). Regarding benefits, 113 chairpersons (60%) considered added psychological counselling to be a direct benefit, while participant payment was considered a direct benefit by 10% (n =19).

They concluded that application of the federal risk and benefit categories for paediatric research was variable and sometimes contradicted by the available data on risks and the regulations themselves.

Thomson, R. Edwards, A. Grey, J. (2005). Risk communication in the clinical consultation. *Clinical Medicine, Journal of the Royal College of Physicians*. 5: 465 - 469.

This article seeks to summarise the state of knowledge of risk communication. Although addressing risk in the clinical context this article can give some guidance for research:

- identify the patients fears;
- be sympathetic;
- risk has 'likelihood' and 'consequence' which both need explanation.

Interestingly, the authors provide evidence that there is little support to the idea that subjects or patients prefer risk expressed in term of other every day (or unlikely) happenings e.g. road traffic accident, lightening strikes.

When expressing risk:

- beware of 'single event probability' – subjects can not have 5% of a stroke;
- beware of relative risks;
- use single denominators where possible;
- graphical presentation can help but needs careful design - an example is presented;
- pilot test presentation of risk;

- think how your subjects might like the information presented.

Paling, J. (2003). Strategies to help patients understand risk. *British Medical Journal*. **327**: 745 - 748.

- Supplement words with numbers;
- use absolute numbers;
- use visual aids where possible;
- check that the a patient has turned data into understanding.

Calman K. (2002). Communication of risk: choice, consent and trust. *Lancet*. **360**: 166 - 168.

Adrian, E. Unigwe, S. Elwyn, G. Hood, K. (2003). Effects of communicating individual risks in screening programmes. *British Medical journal*. **327**: 703 - 709.

A meta-analysis of studies looking how to convey risk.

Nurock, S. (2005). Patients may be less risk averse than committees. *British Medical Journal*. **330**: 471 - 472.

The author believes that ethics committees are putting up barriers to much needed research. As a former carer for her husband, who developed Alzheimer's disease in his fifties, she argues that some people with dementia and their carers perceive acceptable risk differently from ethics committees and are more willing to take risks, feeling there is little to lose. She argues further that research has shown that carers and people with dementia are particularly altruistic in their desire to be included in research.

O'Connor, A.M. Légaré, F. Stacey, D. (2006). Risk communication in practice: the contribution of decision aids. *British Medical Journal*. **327**: 736 - 740.

A discussion of decision aids in clinical practice.

Horrobin, D.F. (2003). Are large clinical trials in rapidly lethal diseases usually unethical? *Lancet*. **361**: 695 - 697.

This moving article is written by a past biomedical researcher who recently developed mantle cell lymphoma, a life threatening malignancy with life expectancy of two to three years. From this point of view he argues that most people are more interested in therapy offering the remote chance of a cure, rather than the certainty of toxicity and the near certainty of a small response. He continues to propose that 50 years ago good scientific evidence of a potential therapeutic effect from a compound, even if only on theoretical grounds, would have quickly generated small clinical trials with little expense. These would have missed marginal but not large effects. It is the latter, he argues, that people in his position want. His view of the medical world is that this is now impossible. Requirements of ethics committees, clinical trial regulations and research costing make such ventures prohibitively expensive, and as a consequence scores of compounds with potential therapeutic benefit will never be tested. This he argues is an unethical situation. The way forward is to undertake small studies, testing a wide range of compounds and looking for significant effects. The present approach of a small number of large studies capable of determining small effects is not what patients want. They wish for cure, not brief life extension at the cost of toxicity.

Edwards, A. Elwyn, G. Gwyn, R. (1999). General practice registrar responses to the use of different risk communication tools in simulated consultations: a focus group study. *British Medical Journal*. 319: 749 - 752.

The authors conducted this study to pilot the use of risk communication tools in simulated general practice and assess the responses of trainee general practitioners in training to these new consultation aids. Both doctors and patients found it helped communication. There were concerns about the lack of available, unbiased, and applicable evidence and a shortage of time in the consultation to discuss treatment options adequately. Graphical presentation of information was often favoured - an approach that also has the potential to save consultation time.

Edwards, A. Elwyn, G. Mulley, A. (2002). Explaining risks: turning numerical data into meaningful pictures. *British Medical Journal*. 324: 827 - 830.

The authors discuss whether the shift towards a greater use of information in consultations is helpful and summarise the current literature on risk communication. They also explore how information can be used without losing the benefits that are traditionally associated with the art, rather than the science, of medicine:

- patients often desire more information than is currently provided;
- communicating about risks should be a two way process in which professionals and patients exchange information and opinions about those risks;
- professionals need to support patients in making choices by turning raw data into information that is more helpful to the discussions than the data;
- 'decision aids' can be useful as they often include visual presentations of risk information and relate the information to more familiar risks.

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## **ANNEX N**

### **INCIDENTAL DISCOVERY OF PATHOLOGY**

#### **How should such incidents be handled?**

#### **1. Summary**

Published articles demonstrate that in some research this is a real issue and researchers need to consider the possibility of the problem arising. Publications offer potential solutions.

#### **2. Evidence**

Illes, J. Kirschen, M. Karetsky, K. Kelly, M. Saha, A. Desmond, J. Raffin, T. Glover, G. Atlas, S. (2004). Discovery and disclosure of incidental in neuro imaging research. *Journal of Medical Resonance Imaging*. **20**: 743 - 747.

In this survey, 82% of brain imaging researchers had unearthed incidental findings and 2-8% of research subjects had clinically significant findings (tumours, malformations).

#### ***People have proposed solutions***

Pickard, J. D. Gillard, J.H. (2005). Guidelines reduce the risk of brain-scan shock *Nature*. **435**: 17.

‘All volunteers are offered counselling which includes discussion of what will happen should an abnormality be detected...’ Our information form includes... ‘there is a chance of less than one in a 100 that your MR scan will show a significant abnormality of which you are unaware. In such circumstances... you will be referred to the appropriate specialist in consultation with your general practitioner, if that is what you would like. Such detection has the benefit of starting treatment early but in a small number of cases may have implications for future employment and insurance.’

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## **ANNEX O**

### **GENETIC TESTING**

For a genetic sub-study to a main study, the participant should be able to refuse participation, but still take part in the main study. Consider how best to facilitate this.

Documents should explain clearly:

- the background and purpose of the genetic study;
- what samples are required and what analyses are planned;
- whether there could be any results of individual significance to the participant and whether it is planned/possible to make feedback available to the participant;
- any implications, e.g. inherited risk, reproductive decisions, insurance status, etc, should be explained, together with what counselling support would be given. It may be necessary to refer the participant for re-testing by genetic services outside the study. The participant must retain the right to choose whether to access this information. If there will be no reliable information of individual significance, this should be explained;
- whether samples are to be kept for future analyses in conjunction with the planned project and whether later feedback could be available(consented);
- that if samples and information are to be retained, the same information as for other biological samples should be given;
- that if there may be later genetic studies then either additional consent will be sought from the participants or the study will be presented to an ethics committee for consideration. Feedback possibilities must again be considered;
- that if there is any likelihood of commercial significance, the participants would not benefit financially;
- the arrangements, if any, for transfer of samples outside of the UK.

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## **ANNEX P**

### **XRAYS/RADIATION**

#### **1. Summary**

There is clear consensus that radiation at moderate to high dose increases the risk of cancer but it is not clear that radiation at low dose (that that would be proposed in medical research) is harmful. The Health Protection Agency advises caution and proposes that it should be assumed that any radiation dose might be a risk, albeit small.

#### **2. Evidence**

Ernst, M. Freed, M.E. Zametkin, A.J. (1998). Health Hazards of Radiation Exposure in the Context of Brain Imaging research: Special Consideration for Children. *Journal of Nuclear Medicine*. 39: 689 – 698.

In this broad literature review of radiation and possible harm, health risks from low level radiation (below 10 rem (0.1 Sv)) - the level most research studies would not exceed) could not be detected above the noise of adverse events of everyday life. The authors concluded that you can not quantify risk below this level.

Cox, R. Muirhead, C.R. Stather, J.W. Edwards, A.A. Little, M.P. (1995). Risk of Radiation-Induced Cancer at Low Doses and Low Dose Rates for Radiation Protection Purposes. Health Protection Agency. Volume 6, No. 1

'It is concluded, therefore, that...at low doses and dose rates, the risk of induced neoplasia rises as a simple function of dose and does not have a DNA damage or DNA repair related threshold-like component...These mechanistic studies, in addition to the epidemiological information, indicate that for radiation protection purposes there is little basis for arguing that low radiation doses (about 10 mGy) would have no associated cancer risk and that, in the present state of knowledge, it is appropriate to assume an increasing risk with increasing dose.'

### Health Physics Society 1996 Health Physics 70 749

The Health Physics Society advise against quantitative estimation of health risk below an individual dose of 5.0 rem in one year. Below 10.0 rem (lifetime dose) (which includes occupational and environmental exposures), risk of health effects are either too small to be observed or are non-existent.

Picano, E. (2004). Sustainability of medical imaging. *British Medical Journal*. 328: 578 – 580.

‘Current radiation protection standards and practices are based on the premise that any radiation dose, no matter how small, can result in detrimental health effects. These include long term development of cancer and genetic damage. These estimates are, however, clouded by approximations and uncertainties for values below 50 mSv, leaving room for conflicting theories that a little radiation could even be beneficial (the hormesis theory) or that current risk estimates might be underestimates.’

The author proposes that, ‘until the controversy is resolved, physicians must minimise radiation exposure by following the ‘do not harm’ and ‘as low as reasonably achievable’ principle.

### **3. Guidance**

National Radiological Protection Board. (2001). X-rays how safe are they? Last accessed at: [http://www.hpa.org.uk/radiation/publications/misc\\_publications/x-ray\\_safety\\_leaflet.pdf](http://www.hpa.org.uk/radiation/publications/misc_publications/x-ray_safety_leaflet.pdf)

The National Radiation Protection Board, College of Radiographers, Royal College of Radiologists and Royal College of General Practitioners have prepared this guidance for clinicians. A useful guide for patients and participants to consider any risk of radiation. It works from the one in three risk we all have of developing cancer and the additional risk that any investigation might place on us.

The radiation risks for simple x-ray examinations of the teeth, chest or limbs, fall into the negligible risk category (less than 1 in 1,000,000 risk). Higher dose examinations such as barium enemas, CT body scans or isotope bone scans fall into the low risk category (1 in 10,000 to 1 in 1,000 risk).

'As we all have a one in three chance of getting cancer even if we never have an x-ray, these higher dose examinations still represent a very small addition to this underlying cancer risk from all causes.'

EXAMINATION	BACKGROUND EQUIVALENT	RISK
Chest Teeth Hands and feet	A few days	Negligible less than 1 in 1,000,000
Skull Head Neck	A few weeks	Minimal 1 in 100000 to 1 in 100000
Breast [mammography] Hip Spine Abdomen Pelvis CT scan of head (Lung isotope scan) (Kidney isotope scan)	A few months to a year	Very low 1 in 100,000 to 1 in 10,000
Kidneys and bladder [IVU] Stomach – barium meal Colon – barium enema CT scan of chest CT scan of abdomen (Bone isotope scan)	A few years	Low 1 in 10,000 to 1 in 1,000

Most people would regard activities involving a risk of below one in 1,000,000 as exceedingly safe. These risk levels represent very small additions to the one in three chance we all have.

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## **ANNEX Q**

### **RESEARCH AND POTENTIAL PREGNANCY**

#### **1. Summary**

If they are to benefit from research, women need to be included in research studies. However precautions are required to minimise the possibility of injury to fertility or the fetus. The scientific review must evaluate the risk to women and their unborn child and the committee needs to assure itself that any risks identified by the scientific review are adequately explained to potential participants.

Consideration also needs to be given to consequences for male fertility.

#### **2. Evidence**

***It isn't a new consideration!***

Mons, G (1751 - 1752). Observations on the Effects of the Vitrum Antimonii Ceratum. *Philosophical Transactions of The Royal Society*. **47**: 273-278.

'Antimony mixed with yellow wax and heated over flame...I should never have ventured to give this medicine to pregnant women if chance had not convinced that it is not more dangerous... for among several women I cured of bloody fluxes there were some, that were actually with child. They were all cured and no accident happened to them. In pursuance I thought I might try it with all imaginable precautions even on sucking children. The medicine succeeds equally well in uterine evacuations.'

Mirkin, B.L. (1975). Drug therapy and the developing human: Who cares? *Clinical Research*. **23**: 106 - 113.

'This policy reflects a choice made between two undesirable outcomes. Society may choose to forbid a drug evaluation in pregnant women and children. This choice would certainly reduce the risk of damaging individuals through research. However, this would maximise the possibility of random disaster resulting from the use of inadequately investigated drugs. In the final analysis it seems safe to predict that more

individuals would be damaged; however the damage would be distributed randomly rather than imposed upon pre-selected individuals.'

Bush, J.K. (1994). The industry perspective on the inclusion of women in clinical trials. *Academic Medicine*. 69: 708 - 715.

The author emphasizes that while women are currently included in clinical trials, more effort must be made to include them in ways that will provide more appropriate and specific information (for example, by including them in earlier phases of trials when possible) and to perform proper analyses that take into account factors of gender and age. Although it is generally agreed that there needs to be more emphasis on determining how to study drugs that may be important for use in women, there is no consensus on what the appropriate proportion of women in trials should be or how early young women should and can be included in trials. The strategies to answer the need for more data about women must be supported by a clear scientific rationale rather than fashioned to meet arbitrary quotas. She concludes with a summary of the key issues affecting women's participation in trials, a list of suggested strategies for the inclusion of women in trials, and an indication of areas where further discussion and resolution are needed.

### **3. Guidance**

Council for International Organizations of Medical Sciences (CIOMS) / World Health Organisation (WHO). (1993). International Ethical Guidelines for Biomedical research involving human subjects. Geneva.

Women...have been discriminated against with regard to their involvement in research...owing to concern about undetermined risks to the fetus. This report proposes that this lack of knowledge could be dangerous. Thalidomide caused more extensive damage than it would have had its first administration been in the context of a trial!

Bennett, J.C. (1993). Inclusion of women in clinical trials - policies for population subgroups. *New England Journal of Medicine*. 329: 288 – 292.

Recruitment of women into non-therapeutic research.

Council for International Organizations of Medical Sciences (CIOMS) / World Health Organisation (WHO). (1993). International Ethical Guidelines for Biomedical research involving human subjects. Geneva.

Pregnant or nursing women should in no circumstances be the subjects of non-clinical research unless the research carries no more than minimal risk to the fetus or nursing infant, and the object of the research is to obtain new knowledge about pregnancy and lactation. As a general rule pregnant or nursing women should not be the subjects of any clinical trial except such trials for which women who are not pregnant or nursing would not be suitable subjects.

Examples of wording to explain the risk of harm to the unborn child:

For women:

*Please share this information with your partner if it's appropriate.*

*The treatment might harm the unborn child; therefore you should not take part in this study if you are pregnant, breast-feeding or you may become pregnant during the study period. If you could become pregnant, you will be asked to have a pregnancy test (urine or blood) before taking part. You must agree to use a reliable form of contraception during the trial, e.g. oral contraceptive and condom, intra-uterine device (IUD) and condom, diaphragm with spermicide and condom.*

*This should be continued for at least \_\_\_ months after the treatment has finished.*

*If you do become pregnant during the course of the study, we would ask you to tell your study doctor immediately so we can help decide appropriate action. We would discuss referral for specialist counselling on the possible risks to your unborn baby and arrangements will be offered to monitor the health of both yourself and your unborn baby. The pharmaceutical company may also request your consent to collect information about your health and that of the baby.*

For men:

*Please share this information with your partner if it's appropriate.*

*It is (or is not) known if the study medicine will affect sperm or semen and therefore you should not father a child during this study or for a safety period of \_\_\_\_months after treatment. If your partner might become pregnant you must use reliable forms of contraception during the trial and for ....months afterwards, e.g. oral contraceptive and condom, intra-uterine device (IUD) and condom, diaphragm with spermicide and condom.*

*If your partner becomes pregnant during the study or within \_\_\_\_months of stopping treatment, you should inform your study doctor immediately.*

*As the risk to your partner and baby is unknown, it is desirable for your partner to agree to medical supervision during her pregnancy and for the baby after it is born. Your study doctor will work with the sponsoring company to organise this. Your partner will be invited to sign a consent form to allow medical supervision. The pharmaceutical company may also request you and your partner's consent to collect confidential information about her health and that of the baby.*

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## **ANNEX R**

### **THE CONSEQUENCES OF RESEARCH**

#### **Do participants benefit from research?**

##### **1. Summary**

Some studies purport to show a trial benefit but a recent meta-analysis could not support this and demonstrated significant methodological problems in previous work. It seems the majority of those who participate find it a positive experience, but it is probably best to refrain from claiming any therapeutic benefit simply from being in a study.

##### **2. Evidence**

Schmidt, B. Gillie, P. Caco, C. Roberts, J. Roberts, R. (1999). Do sick newborn infants benefit from participation in a randomized clinical trial? *Journal of Pediatrics*. **134**: 151 – 155.

These authors looked at new born babies who would have been eligible for a trial of lung surfactant but were not enrolled. Length of ventilation was significantly shorter in the placebo treated group when compared to these (un-enrolled) babies.

Albert, S.M. Sano, M. Marder, K. (1997). Participation in clinical trials and long-term outcomes in Alzheimer's disease. *Neurology*. **49**: 38 - 43.

Of 215 community-resident subjects, 101 participated in randomised clinical trials during the first two years of follow-up. These subjects were compared with subjects who met eligibility requirements for randomised control trials (RCTs) but did not participate and with subjects who were ineligible, over a total of 3.5 years of follow-up. Subjects who participated in RCTs were younger and more highly educated. Mortality, risk of hospitalization, number of medical examinations conducted by study physicians, and onset of severe functional deficit did not differ between the groups, but risk of nursing home admission was significantly lower among RCT participants compared with eligible non participants and ineligible subjects. The authors recognise that this

may be attributed to many factors and could not be definitely attributed to trial participation.

Peppercorn, J. M. Weeks, J. C. Cook, E. F. Joffe, S. (2004). Comparison of outcomes in cancer patients treated within and outside clinical trials: conceptual framework and structured review. *Lancet*. **363**: 263 – 270.

The authors conducted a meta-analysis of 23 studies to assess any 'trial effect.' They concluded that there are insufficient data to say that such an effect exists, contrary to much professional opinion who hold that trial participation on its own has benefit. No evidence was found to suggest participation led to harm.

Vist, G.E. Hagen, K.B. Devereaux, P. Bryant, D. Kristoffersen, D.T. Oxman, A.D (2005). Systematic review to determine whether participation in a trial influences outcome. *British Medical Journal*. **330**: 1175 – 1179.

No strong evidence was found of a harmful or beneficial effect of participating in RCTs compared with receiving the same or similar treatment outside such trials.

Participation in non therapeutic studies may be beneficial

Dyregrov, K. (2004). Bereaved parents' experience of research participation. *Social Science and Medicine*. **58**: 391 - 400.

Sixty-four parents who had lost a child completed a short questionnaire evaluating research participation. The authors found that 100% of the parents experienced participation as 'positive'/'very positive', and none regretted participating. They linked the positive experiences to being allowed to tell their complete story, the format of the interview, and a hope that they might help others. However, three-quarters of the interviewees reported that it was to a greater or lesser degree painful to talk about the traumatic loss.

Terry, W. Olson, L.G. Ravenscroft, P. Wilss, L. Boulton-Lewis, G. (2006). Hospice patients' views on research in palliative care. *Internal Medicine Journal*. **36**: 406 – 413.

Twenty-two patients admitted to a hospice participated in semi structured interviews. All the patients wanted to participate in research and advanced one or more reason for

participation, the commonest being altruism. They valued the commitment by doctors to optimising care by research. They rejected the view that their consent might be non-autonomous and put forward consistent views about what they considered relevant to consent. The patients did not share the concerns of ethicists about the difficulties and hazards of research with the terminally ill. The authors concluded, 'these patients' views are not reflected in the professional consensus.'

American Association for Public Opinion Research (2005). Protection of human participants in survey research: a source document for institutional review boards. Last accessed at: <http://infohost.nmt.edu/~red/IRB/AAPORdoc.pdf>

Many survey participants report that they enjoy the survey process. This enjoyment and the sense of good feeling they get from helping the research enterprise makes surveys possible. The pleasure is probably temporary; no systematic evidence of long-term benefits from survey participation has been collected, though such benefits are possible.

Jacomb, P.A. Jorm, A.F. Rodgers, B. Korten, A.E. Henderson, A.S. Christensen, H. (1999). Emotional response of participants to a mental health survey. *Social Psychiatry and Psychiatric Epidemiology*. **34**: 80 – 84.

2725 adults who participated in a mental health survey were asked further questions about their feelings after participation. 5% felt distressed, 3% depressed, 3% were concerned about privacy yet 35% reportedly felt good about themselves!

The authors reviewed other similar work and report that these other studies found similar results. (Turnbull *et al* (1988) *American Journal Of Orthopsychiatry*. **58**: 228, Henderson and Jorm (1990) *Psychological Medicine*. **20**: 721, Jorm *et al* (1994) *Psychological Medicine*, **24**: 233 – 237).

Taylor, C. Trowbridge, P. Chilvers, C. (1991). Stress and cancer surveys: attitudes of participants in a case-control study. *Journal of Epidemiology and Community Health*. **45**: 317-20.

The authors sent questionnaires to women aged 20 to 45 with invasive cervical carcinoma who had been interviewed as part of a study into cervical carcinoma. 2/226 regretted participation, while half perceived some benefit. The authors recognised the interview was difficult yet they found little evidence of distress afterwards.

Burnet, K. Benson, K. Earl, H. Thornton, H. Cox, K. Purushotham, A. (2004). A survey of breast cancer patients' views on entry into several clinical studies. *European Journal of Cancer Care*. **13**: 32 - 35.

The authors questioned women with breast cancer treated at their unit who had been asked to participate in clinical trials. Most (around 85%) felt participation was worthwhile. None regretted participation.

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## **ANNEX S**

### **END OF TRIAL ARRANGEMENTS**

#### **What should participants expect at the end of a therapeutic trial?**

##### **1. Summary**

There is continuing debate about the arrangements for subjects and the community at the end of a therapeutic trial, there is little available evidence as to how society sees the problem.

This issue is not straight forward and it may be difficult to decide the fairest option at the end of a study.

Difficulties include:

- studies now rarely provide a definitive **clinical** answer;
- results from large studies may not be available for some time after the first patient has finished the study;
- study medications may not be licensed;
- companies may be legally unable to promote or provide trial medication outside a trial.

Opinion from the 'August Bodies' seems to agree that broad guidance on this issue is impossible and suggest a 'case by case' approach, considering the details of any study on its own merits. Ultimately they leave decisions to the reviewing body.

##### **2. Evidence**

***Studies do not necessarily provide a definitive clinical answer***

Pitt, B. (2004). ACE Inhibitors for patients with vascular disease without left ventricular dysfunction: May they rest in PEACE? *New England Journal of Medicine*. 351: 2115 – 2117.

Polderman, K.H. Girbes, A.R. (2004). Drug intervention trials in sepsis divergent results *Lancet*. **363**: 1721 - 1723.

Results in trials of treatment in sepsis have on occasion produced conflicting results and consequently planning therapy and drawing up guidance can be problematic. This paper illustrates the complexity of scientific advance, and how studies may need to be repeated before their results can be accepted and their conclusions incorporated into clinical care guidelines. Simple models of research and therapeutic advance often promulgated by the media can be misleading and dangerous.

### **3. Guidance**

World Medical Association Declaration of Helsinki. Ethical Principles for Medical Research Involving Human Subjects. <http://www.wma.net/e/policy/pdf/17c.pdf>

'At the conclusion of the study, every patient entered into the study should be assured of access to the best proven prophylactic, diagnostic and therapeutic methods identified by the study.'

But tempers advice:

'The WMA hereby reaffirms its position that it is necessary during the study planning process to identify post-trial access by study participants to prophylactic, diagnostic and therapeutic procedures identified as beneficial in the study or access to other appropriate care. Post-trial access arrangements or other care must be described in the study protocol so the ethical review committee may consider such arrangements during its review.'

Nuffield Council of Bioethics. (2005). The Ethics of Research related to Healthcare in Developing Countries. A follow up discussion paper. London.

'The principle that those in the control arm of a trial should be provided with the intervention when it has been demonstrated to be efficacious is widely acknowledged. We consider that there is an ethical obligation to provide a control group with an intervention when it would benefit them (paragraph 9.24).'

But then reneges on this argument:

'We conclude moreover that it would not be ethically acceptable for any study to begin without a decision having been made about whether or not those in control groups will be offered an intervention shown to be successful on completion of the trial, where relevant and appropriate. Participants should be informed of the decision as part of the process of obtaining their consent.'

And add:

'We take the view that in general, it is the responsibility of governments and not researchers or sponsors to determine the level of healthcare and the range of treatments and medicines that are provided to populations.'

#### The US National Bioethics Advisory Committee

'Researchers and sponsors in clinical trials should make reasonable good faith efforts before the initiation of a trial to secure, at its conclusion continued access for all participants to needed experimental intervention that have been proven to be effective for the participants. Although the details of the arrangements will depend on a number of factors (Including but not limited to the results of the trial) research protocols should typically describe the duration, extent and financing of such continued access. When no arrangements have been negotiated, the researcher should justify to the ethics committee why this is the case.'

Its guidance over broader implementation is ambiguous, recommendation 4:3 states:

'Wherever possible preceding the start of research, agreements should be negotiated by the relevant parties to make the effective intervention or other research benefits available to the host country after the study is completed.'

Although 4:2 suggests:

'In cases in which investigators do not believe that successful interventions will become available to the host country population, they should explain to the relevant ethics review committee why the research is nonetheless responsive to the health needs of the country.'

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## **ANNEX T**

### **CONFIDENTIALITY AND USE OF PERSONAL DATA**

#### **1. Summary**

There is evidence that the public support use of personal data for medical research, preferably but not invariably after consent has been obtained.

Professional guidance is at variance and seems to insist on consent.

Legal positions seem to be contradictory.

#### **2. Evidence**

Willison, D.J. Keshavjee, K. Nair, K. Goldsmith, C. Holbrook, A.M (2003). Patients' consent preferences for research uses of information in electronic medical records. *British Medical Journal*. **326**: 373.

In a Canadian survey of 123 families, broad support for research use of data was found. 74% wished to be consulted, 26% accepted 'passive' use of their data.

Whiteman, D.C. (2006). Australian public's views on privacy and health research. *British Medical Journal*. **332**: 1274.

In a random telephone survey of 301, 192 (64%) were in favour of health databases being used for research.

The Academy of Medical Sciences (2006). Personal Data for Public Good: using health information in medical research. Last accessed at: <http://www.acmedsci.ac.uk/images/project/Personal.pdf>

Chapter 5 (Page 69).

Two large studies are especially noteworthy because of the rigorousness of the methodology and the focus of the questions:

Shickle *et al.* (2002) conducted a study of public opinions of the use of electronic records in healthcare. The findings showed that there were social variations in willingness to share records for health care (men, older people and higher social groups being more willing), that anonymised data were preferred where possible and that the uses to which the data were put was not a strong determining factor in whether participants were happy with data sharing. Participants were more accepting of the need for doctors to see their records than receptionists and social workers. For research there was some definition of research purpose but the enquiry was not explicit with respect to methods of ensuring confidentiality or research regulation so the underlying knowledge of the participants in answering the questions cannot be assessed.

Barrett *et al.* (2006) concentrated on the use of medical records and registration for cancer research. In a large random sample of UK homes participants were given a full explanation of the purpose of the research before being asked their opinion. The great majority of participants supported the use of their personal data for cancer research and registration, provided confidentiality and security were assured. The investigators found that only a small proportion of the public knew of the existence of cancer registries. However, when asked, the great majority supported a law to make cancer registration statutory, (the situation in some other countries).

Jones, C. (2003). The utilitarian argument for medical confidentiality: a pilot study of patients' views. *Journal of Medical Ethics*. 29: 348 - 352.

In a BMA survey 93% of respondents agreed with the comment 'doctors are patients' representatives and therefore should not be expected to release information about a patient to a third party.'

The author conducted a small study using GP patients, presenting short vignettes and asking if, in these conditions, the doctor should break confidentiality. Once given a fairer context it seems that people give different answers. The author concludes 'subjects' views are more complex and that medical confidentiality does not have unqualified support (suggested by the BMA survey).'

Carman, D. Britten, N. (1995). Confidentiality of medical records: the patient's perspective. *British Journal of General Practice*. 45: 485 – 488.

Semi-structured interviews were carried out with 39 patients from one general practice. The majority of interviewees felt that administrative and secretarial staff should not have access to medical records. Some patients had reservations about a doctor not directly involved in their care having access to their records. The authors questioned the assumptions of shared doctor-patient definitions of confidentiality, at least in their practice.

Barrett, G. Cassell, J.A. Peacock, J.L. Coleman, M.P. (2006). National survey of British public's views on use of identifiable medical data by the National Cancer Registry. *British Medical Journal*. 332: 1068 – 1072.

The authors sought to describe the views of the British public on the use of personal medical data by the National Cancer Registry without individual consent using a national cross sectional, face to face interview survey. 72% of all respondents did not consider inclusion of postcode, inclusion of name and address, and the receipt of a letter inviting them to a research study on the basis of inclusion in the registry to be an invasion of their privacy. 81% of all respondents said that they would support a law making cancer registration statutory. They concluded that most of the British public considers the confidential use of personal, identifiable patient information by the National Cancer Registry for the purposes of public health research and surveillance not to be an invasion of privacy.

Peto, J. Fletcher, O. Gilham, C. (2004).Data protection, informed consent, and research. *British Medical Journal*. 328: 1029 - 1030.

At a public meeting in November 2002, the audience were provided with an electronic voting facility. After a discussion of the restrictions on access to medical records that British epidemiologists now face and how that affects their work, the audience were invited to vote for or against the following proposed law: 'Consent is not required for access to medical records for non-commercial medical research that has no effect on the individuals being studied and has been approved by an accredited research ethics committee.' The vote in favour was 93%. The audience included members of the general public, patients' support groups and cancer charities, doctors, nurses, and public health workers.

Iversen, A. Liddell, K. Fear, N. Hotopf, M. Wessely, S (2006). Consent, Confidentiality and the Data Protection Act: Still not getting it right. *British Medical Journal*. **332**: 165 - 169.

The authors looked at their previous data to determine the perception of their past participants to approach and use of data. Refusal varied between 0.06% and 11.3%, with telephone interviews the most difficult. Postal surveys had very low stated refusal rates. They conclude, 'we are not arguing that epidemiological research should always proceed without consent. But it should be allowed to do so when the privacy interference is proportionate' and there is 'a propensity to over predict participants distress.'

Robling, M.R. Hood, K. Houston, H. Pill, R. Fay, J. Evans, H.M. (2004). Public attitudes towards the use of primary care patient record data in medical research without consent: a qualitative study. *Journal of Medical Ethics*. **30**: 104 - 109.

These workers, involving 49 members of the public and four lay representatives in focus groups found a cautious attitude to research using data without consent. The lay representatives were even more cautious (in line with other work that those in a regulatory role will tend to a more conservative attitude (Nurock, 2005)). The authors acknowledge such opinion could not be considered representative and add the caveat at the end of their article that quantitative work is required to determine how widely held these views are.

### **3. Guidance**

#### Professional

Confidentiality is a central consideration in most guidance for health care professionals. It seems to demand that consent is sought from the patient for research.

#### NHS Code of Confidentiality

Patient information is generally held under legal and ethical obligations of confidentiality. Information provided in confidence should not be used or disclosed in a form that might identify a patient without his or her consent. There are a number of

important exceptions to this rule, described later in this document, but it applies in most circumstances.

P 12 - Preventative medicine, medical research, health service management, epidemiology etc are all medical purposes as defined in law. Whilst these uses of information may not be understood by the majority of patients, they are still important and legitimate pursuits for health service staff and organisations. However, the explicit consent of patients must be sought for information about them to be disclosed for these purposes in an identifiable form unless disclosure is exceptionally justified in the public interest or has temporary support in law under section 60 of the Health & Social Care Act 2001.

General Medical Council (2000). Confidentiality—protecting and providing information. London.

‘If consent can not be obtained disclosure may only be made if essential to protect the patient or someone else from risk of death or serious harm.’

#### The ‘Caldicott Principles’

Access to person-identifiable information should be on a strict need-to-know basis. Only those individuals who need access to person-identifiable information should have access to it, and they should only have access to the information items that they need to see. This may mean introducing access controls or splitting information flows where one information flow is used for several purposes.

Political guidance might be seen to be striking a more cautious balance.

Wanless, D. (2004). Securing Good Health for the whole population. Final report. Last accessed at: [http://www.hm-treasury.gov.uk/consultations\\_and\\_legislation/wanless/consult\\_wanless04\\_final.cfm](http://www.hm-treasury.gov.uk/consultations_and_legislation/wanless/consult_wanless04_final.cfm)

Securing Good Health for the whole population (The Wanless’ report 2004) seems to recognise that individual rights must be balanced against the benefit to society that research brings:

Section 9.16 – ‘The White Paper should address the possible threat to public health research, which arises from the difficulty of obtaining access to data because of the

need to strike a balance between individual confidentiality and public health research requirements.'

The law seems to disagree with itself. The data commissioner takes one approach

Walley, T. (2006). Using personal health information in medical research. Overzealous interpretation of UK laws is stifling epidemiological research. *British Medical Journal*. 332: 130 – 131.

The information commissioner has decided that, while obtaining consent for medical research involving identifiable personal health data is the default position, consent is not required where such access to the data is necessary (for example in a research protocol approved by an ethics committee), is considered proportionate and no more with respect to privacy and public interest, and where there is 'fair processing' (meaning that the patient should be informed of the data collection and have the right to opt out). Even informing the patient may be waived if the effort to do so is disproportionate, especially if the research is 'historical or statistical.' Transparency and proportionality are also emphasised in the NHS research governance framework. Many data controllers responsible for the implementation of the Data Protection Act seem unaware that there are reasonable exceptions to the general rule of consent.

Lord Falconer of Thoroton. (2000). *Freedom of information bill (Hansard)*. Column 261-265.

The Data Protection Act 1998 allows medical data to be used for any medical research purpose without the need for the consent of individuals. It is not necessary to define the term 'medical research,' nor to make specific provision for it to include the monitoring of public health, which for these purposes is regarded as medical research. It is clear that many practitioners are confused between the requirements of the Data Protection Act 1998 and those of the various regulatory and representative bodies within the sector.

Information Commissioner. (2002). Use and disclosure of health data: guidance on the application of the Data Protection Act 1998.

...It is a common misconception, for instance, that the Act always requires consent of data subjects to the processing of their data.

Boyd, P. (2003). Health research and the Data Protection Act 1998. *Journal of Health Services Research and Policy*. 8(sup 1): S1 - S7.

The two most widely held misconceptions are that the Act creates an overarching requirement to obtain explicit consent for the processing of all health data and that the requirements of the Act are additional to good professional standards, medical ethics and confidentiality. In fact, in most cases the Act will almost never require consent for the processing of data for research purposes, unless consent is also a more general legal requirement.

However, on its website, the Department of Health writes:

### Background

The Government has made it clear that informed consent is the fundamental principle governing the use of patient identifiable information by any part of the NHS or research community.

### The law

Although this policy direction has an ethical basis, there are important legal considerations. Patients provide information about themselves in confidence and where information is held in confidence, common law provides no other reliable justification other than informed consent for use of the information in a patient identifiable form.

### The problem

There are also situations where informed consent cannot be obtained. For example, important research projects may involve tens of thousands of patients where contact would be impracticable. The essential nature of some of this research means that the public good outweighs issues of privacy. Some patients are not capable of giving consent, but the health service still needs to know about them and their conditions. Sometimes excluding those who refuse consent might bias data collection to the extent that it loses all value.

### The solution

Section 60 of the Health and Social Care Act 2001 provides a power to ensure that patient identifiable information needed to support essential NHS activity can be used without the consent of patients. The power can only be used to support medical

purposes that are in the interests of patients or the wider public, where consent is not a practicable alternative and where anonymised information will not suffice. It is intended largely as a transitional measure whilst consent or anonymisation procedures are developed, and this is reinforced by the need to review each use of the power annually.

Interestingly outside the UK:

Forman, D. Brewster, D. (2006). Protecting the work of UK Cancer Registries. *British Medical Journal*. [Rapid response].20 May 2006. Last accessed at: <http://bmj.bmjournals.com/cgi/eletters/332/7549/1068>

'Several countries, including the USA, New Zealand and Sweden, have primary legislation to ensure 100% registration' (in Cancer Registries).

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## **ANNEX U**

### **DATA STORAGE**

#### **Ethically, how long can data be stored?**

##### **1. Summary**

Guidance conflicts and concentrates on the definition of a minimum time data should be stored, rather than a maximum. There is little evidence on the public's viewpoint.

Funders increasingly require researchers to file their data and allow access to others after a fair period. The research community feels this allows better use of any research data.

It would seem therefore that data should be stored while they may have a potential use and this stance would meet funders' requirements. The REC should ensure that the possibility of malign or accidental disclosure is minimised.

##### **2. Evidence**

###### ***An example of the value of re-analysis of data***

Krewski, D. Burnett, R.T. Goldberg, M.S. Hoover, K. Siemiatycki, J. Jerrett, M. Abrahamowicz, M. White, W.H. (2000). Reanalysis of the Harvard Six Cities Study and the American Cancer Society Study of particulate air pollution and mortality. Cambridge, MA: Health Effects Institute.

The authors re-analysed the data collected in:

Dockery, D.W. Pope, C.A. Xu, X. Spengler, J.D. Ware, J.H. Fay, M.E. Ferris. B.G. Speizer, F.E. (1993). An association between air pollution and mortality in six U.S. cities. *The New England Journal of Medicine*. **329**: 1753 – 1759.

Access to these data enabled the researchers to add support to the original conclusions using more up to date statistical analysis.

### 3. Guidance

General Medical Council (UK) (<http://www.gmc-uk.org>)

The UK General Medical Council, suspended a researcher when he failed to maintain complete and accurate records and retain them for audit. Guidance from this body to researchers is to record research results accurately, keep the records secure, and consult with all the other authors when submitting the work for publication.

Grigg, J. (2005). Good Research Conduct. *Archives of Disease in Childhood*. 90: 229 - 232.

An additional requirement demanded by research councils, universities, and some journals, is that research data should be retained for at least five years (whether current clinical researchers could reconstruct their five year old publications using original data, is debatable). It is therefore the responsibility of all authors of a publication, to ensure that data are stored and formatted.

The 'EU Directive on GCP' 2005/28/EC

'The sponsor and the investigator shall retain the essential documents relating to a clinical trial for at least five years after its completion. They shall retain the documents for a longer period, where so required by other applicable requirements or by an agreement between the sponsor and the investigator. Essential documents shall be archived in a way that ensures that they are readily available, upon request, to the competent authorities. The medical files of trial subjects shall be retained in accordance with national legislation and in accordance with the maximum period of time permitted by the hospital, institution or private practice.'

In addition, CPMP/ICH/135/95 (Note for Guidance on Good Clinical Practice) suggests that documents specific to the sponsor should be retained for at least two years after the last approval of a marketing application in an ICH region, and until there are no pending or contemplated marketing applications in an ICH region, or at least two years after the formal discontinuation of clinical development of the IMP. The sponsor should inform the investigator/institution in writing of the need for retaining records and should notify the investigator/institution in writing when records relating to the trial are no longer needed. So the minimum length of time for all trials is five years after the trial

has finished (GCP directive). For trials used to support marketing authorisations it could be significantly longer but no maximum time limit is stated.

Department of Health (1999). HSC 1999/053: For the record - managing records in NHS Trusts and health authorities. Last accessed at:

<http://195.33.102.76/assetRoot/04/01/20/36/04012036.pdf>

This stipulates storage for 15 years after conclusion of treatment.

Medical Research Council (UK) (<http://www.mrc.ac.uk>)

The MRC (UK) advice in 'Good Research Practice' is that:

'Retaining data:

Retention of accurately recorded and retrievable results is essential for research.

Primary research data (and where possible, relevant specimens, samples, questionnaires, audio-tapes, etc.) must be retained in their original form within the research establishment that generated them for a minimum of ten years from completion of the project.'

Other Research Councils share this view and that ALL research data must be offered for sharing via a central archive.

Gene Therapy Advisory Council (GTAC).

The Gene Therapy Advisory Council stipulates that material obtained in studies they have approved should be retained indefinitely.

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## **ANNEX V**

### **SAMPLES**

#### **1. Summary**

The majority of public and patients are prepared to give samples for research.

#### **2. Evidence**

Start, R.D. Brown, W. Bryant, R.J. Reed, M.W. Cross, S.S. Kent, G. Underwood, J.C.E. (1996). Ownership and uses of human tissue. *British Medical Journal*. **313**: 1366 – 1368.

Amongst 384 surgical patients there was strong support for the use of tissue in medical education, research and science except when tissues might transmit infection. There was at that time confusion amongst this group as to who, if anyone, owned the tissue.

##### **Results - Use of tissue in:**

	<b>Yes</b>	<b>No</b>
Teaching	332	6
Diagnostics	327	7
Research	319	6
Testing new treatment	273	24
Testing new drugs	252	27

Stegmayr, B. Asplund, K. (2002). Informed consent for genetic research on blood stored for more than a decade. *British Medical Journal*. **325**: 634 – 635.

Of 1409 patients approached for their blood to be used in a genetic research ten years after donation, 93% consented provided REC had approved the study, 31 objected (2.2%), 64 did not reply and three provided incomplete answers. The researchers found no great difficulty gaining consent and report no distress caused.

Furness, N. Nicholson, M.L. (2004). Obtaining explicit consent for the use of archival tissue samples: practical issues. *Journal of Medical Ethics*. 30: 561 – 564.

The authors discuss the problems of obtaining consent for research on archived biopsy tissue. UK sources (Department of Health, Medical Research Council) propose consent should be sought for research on archived material, unless unethical or impractical.

To study public attitudes, 495 letters were sent to patients believed to be recipients of kidney transplants to seek consent for further research on samples taken from their kidney transplant in routine clinical care. 328 (68%) were returned; 316 gave consent, 12 objected (3.6%). Despite careful scrutiny, contact caused upset in at least 13 cases. Of the non-responders (159), 33 could be contacted through out patients. Thirty-two gave consent, one objected. The authors argue that insistence on consent would have prevented research on 255 of the patient population who would have agreed to the work, and look through the literature to demonstrate the views of their patient group are in line with other work.

Hoeyer, K. Olofsson, B.O. Mjörndal, T. Lynöe, N. (2005). The Ethics of Research using Biobanks. *Archives of Internal Medicine*. 165: 97 – 100.

The authors investigated donors' perceptions of consent procedures of a Swedish tissue bank using a questionnaire sent to a randomized sample of 1200 donors who had donated blood and signed informed consent forms. The response rate was 80.9%. Of those that recalled consent 90% were content with consent. 85.9% accepted the process whereby further research could go ahead without further consent provided it had been reviewed by a research ethics committee.

Jack, A.L. Womack, C. (2003). Why surgical patients do not donate tissue for commercial research. *British Medical Journal*. 327: 262.

In fact they do. In 3140 preoperative interviews, 3102 (98.8%) consented while only 38 (1.2%) refused to allow their tissue to be used for commercial research. When patients have adequate information, donating surgically removed human tissue to biomedical research in the commercial sector is not a contentious issue. The consent process is facilitated by face to face interviews with a trained nurse.

McQuillan, G. Porter, K.S. Agelli, M. Kington, R. (2003). Consent for genetic research in a general population: The NHANES experience. *Genetics in Medicine*. 5: 35 – 42.

The authors analysed the characteristics of consenting individuals participating in the US National Health and Nutrition Examination Survey, a nationally representative survey of the US household population. In 1999, 84% of eligible participants consented to have their blood samples included in a national repository for genetic research. In 2000, 85.3% consented. Females and black participants in both years were least likely to consent (1999, 82.2% and 73.2%; 2000, 83.6% and 81.3%, respectively).

Wendler, D. Emanuel, E. (2002). The debate over research on stored biological samples: what do sources think? *Archives of Internal Medicine*. 162: 1457 – 1462.

Data were gathered using a telephone survey of 504 individuals living in the United States. Two cohorts were studied: (1) individuals who had participated in clinical research and contributed biological samples and (2) randomly selected Medicare recipients. Of the respondents, 65.8% would require their consent for research on clinically derived, personally identified samples; 27.3% would require it for research on clinically derived samples that are 'anonymized.' For research - derived samples, 29% of the respondents would require their consent if the samples retain personal identifiers.

Chen, D.T. Rosenstein, D.L. Muthappan, P. Hilsenbeck, S.G. Miller, F.G. Emanuel, E.J. Wendler, D. (2005). Research With Stored Biological Samples: What Do Research Participants Want? *Archives of Internal Medicine*. 165: 652 – 655.

The authors analysed 1670 consent forms signed by research participants that offer options for future research with participants' biological samples. They were healthy volunteers, family members of affected individuals, and individuals with a broad range of medical conditions enrolled in clinical research studies with and without the prospect of direct medical benefit. 87.1% of research participants given the option chose to authorize future research on any medical condition. More than 85% permitted unlimited future research with their stored biological samples regardless of sex, age, geographic location, or whether the individual was affected by the disease being studied or a healthy volunteer. Only 6.7% of those given the option to refuse all future research did so. Although African Americans were less likely to permit future research, 75% of African Americans still authorized unlimited future research with their samples.

Kettis-Lindblad, A. Ring, L. Viberth, E. Hansson, M.G. (2006). Genetic research and donation of tissue samples to biobanks. What do potential sample donors in the Swedish general public think? *European Journal of Public Health*. **16**: 433 - 440.

This was a cross-sectional survey of a random sample of the general public in Sweden, (n - 6000) (response rate 49.4%) to identify perceptions of the general public regarding research involving human tissues to assess the public's willingness to donate samples to biobanks and to identify factors associated with the willingness to donate samples. A majority of the respondents had a positive attitude towards genetic research. Their trust in authorities' capability to evaluate the risks and benefits of genetic research varied. Individual university/hospital-based researchers received the greatest trust, while the county councils (health care providers), and the Swedish Parliament received the lowest trust. Most respondents (86%) would donate a linked blood sample for research purposes. Another 3% would provide an anonymous sample. In total, 78% of the respondents would agree to both donation and storage. The most common motive was benefit of future patients. The majority was indifferent to the funding source for the research and would delegate this judgment to the research ethics committee. They concluded that the majority of the general public is willing to donate a sample to a biobank. The willingness is mainly driven by altruism, and depends on the public being well-informed and having trust in experts and institutions.

### **3. Guidance**

Medical Research Council (UK) (2001). Human Tissue and Biological Samples for use in Research. Operational and Ethical Guidelines. Last accessed at:  
<http://www.pre.ethics.gc.ca/english/pdf/links/HumanTissueandBiologicalSamplesforuseinResearch.pdf>

Ownership and Custodianship: The legal position in relation to uses of human tissue was discussed in detail in the Nuffield Council on Bioethics Report 'Human Tissue: Ethical and Legal Issues (1995).' 'We recommend that tissue samples donated for research be treated as gifts or donations, although gifts with conditions attached. This is preferable from a moral and ethical point of view, as it promotes the 'gift relationship' between research participants and scientist .and underlines the altruistic motivation If samples taken for research are to be treated as gifts, there must be a recipient, to whom formal responsibility for custodianship of a donated sample of material is

transferred. ...The university, hospital or other host institution where the principal investigator is based will usually be the most appropriate body to have formal responsibility for custodianship of human material donated for research, When consent is obtained, the donor (or the person giving consent in the case of material obtained after death) needs to understand that he/she is making a donation of the sample for use in research.'

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## **ANNEX W**

### **INFORMING PARTICIPANTS OF RESULTS**

#### **What should participants be told?**

##### **1. Summary**

Research indicates that some but not all subjects wish to hear the results of research.

Researchers need to think separately about individual and general feedback and caution is needed in some cases.

Research studies rarely provide a definitive answer to a therapeutic question, rather they add to a larger 'debate' which develops into a consensus when results from other trials are incorporated.

##### **2. Evidence**

Research indicates that subjects wish to hear the results of research.

Richards, P.M. Ponder, M. Pharoah, P. Everest, S. Mackay, J. (2003). Issues of consent and feedback in a genetic epidemiological study of women with breast cancer. *Journal of Medical Ethics*. 29: 93 - 96.

The authors provide a report from participants in the UK Anglian Breast Cancer Study (ABC). Participants' attitudes to feedback of information, reasons for participation, confidentiality, and to the wider use, of the data and DNA were explored. At the time 1484 women had been enrolled. Of those enrolled in the study the majority (93%) indicated that they wished to be informed if something were found. 21 were interviewed. The most common reasons given for taking part was to help others and the importance of cancer research. Many mentioned their own family and the potential help the study might give to their sisters or daughters. All, when asked, said they felt there ought to have been some general feedback about the outcomes of the study. A minority felt very strongly about this.

Dixon-Woods, M. Jackson, C. Windridge, K.C. Kenyon, S. (2006). Receiving a summary of the results of a trial: qualitative study of participants' views. *British Medical Journal*. **332**: 206 – 210.

Twenty women (of 9,000 in the UK) who had participated in the ORACLE trial of antibiotics for pre-term labour and pre-term rupture of the membranes and requested a copy of the trial results took part in a semi structured interview to discuss the feedback of results.

General feedback: Less than a fifth of women who participated in the ORACLE trial indicated that they wished to receive the trial results. Reactions to the leaflet summarising the trial results were generally positive or neutral, although some women had difficulty in understanding the leaflet, and there was evidence of possible negative implications for women who had adverse outcomes.

Individualised aspects: Women (in this small group) wished to know to which arm of the trial they had been allocated and the implications for their own pregnancy. Some were disappointed with receiving a generic summary and their accounts indicated some confusion about the trial findings

Snowdon, C. Garcia, J. Elbourne, D. (1998). Reactions of participants to the results of a randomised controlled trial: exploratory study. *British Medical Journal*. **317**: 21 – 26.

The authors assessed views of parents of babies who participated in a neonatal trial, about feedback of trial results. Discussion with parents of 24 surviving babies enrolled in a UK randomised controlled trial comparing ventilatory support by extracorporeal membrane oxygenation with conventional management revealed information about mortality was well understood but morbidity was less clearly reported. Even when the content was emotionally exacting, the information was still wanted. They concluded that feedback of trial results to participants should be a consideration of researchers, but a careful approach is required. This study was based on a highly selective group of parents within a particularly sensitive trial.

Their 'key messages' were:

- feedback of results of randomised controlled trials can be part of an open and inclusive approach to participation in medical research;

- the procedure for offering feedback should be considered at the start of a trial;
- results should only be sent to people who respond positively to such an offer, and particular attention paid to feedback to potentially vulnerable groups;
- the effect of feedback of sensitive information needs evaluation in a variety of contexts;
- research studies rarely provide a definitive answer to a therapeutic question, rather they add to a larger 'debate' which develops into a consensus incorporating results from other trials.

Pitt, B. (2004). ACE Inhibitors for patients with vascular disease without left ventricular dysfunction: May they rest in PEACE? *New England Journal of Medicine*. **351**: 2115 – 2117.

Polderman, K.H. Girbes, A.J. (2004). Drug intervention trials in sepsis: divergent results. *Lancet*. **363**: 1721 – 1723.

Results in trials of treatment in sepsis have on occasion produced conflicting results that have been difficult for the research and medical community to resolve. Consequently planning therapy and drawing up guidance can be problematic. This paper illustrates the complexity of scientific advance, and how studies may need to be repeated before their results can be accepted and their conclusions incorporated into clinical care guidelines. Simple models of research and therapeutic advance often promulgated by the media can be misleading and dangerous.

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## **ANNEX X**

### **TRIAL REGISTRATION**

#### **Why should researchers be encouraged to register their study?**

##### **1. Summary**

There is strong support for this, and drug trials that are not registered should be questioned. Such registration allows access for meta-analyses and goes some way to redressing the well recognised bias toward publishing positive trials. Proponents of trial registration argue that not registering trials undermines public health.

##### **2. Evidence**

Publication bias

Chalmers, I. (2006). From optimism to disillusion about commitment to transparency in the medico-industrial complex. *Journal of the Royal Society of Medicine*. 99: 337 -341.

The author argues that patients' lives are being put at risk because drug firms cannot be trusted to publish unbiased clinical research. He suggests ways to increase confidence in the scientific integrity of the pharmaceutical industry.

Decullier, E. Lh eritier, V. Chapuis, F. (2005). Fate of biomedical research protocols and publication bias in France. *British Medical Journal*. 331: 19.

Questionnaire study looking at 649 protocols presented to French RECs. 581 (90%) were started, 501 (86%) completed but only 190 (38%) were published. Positive studies were four times more likely to be published.

Simes, R.J. (1986). Publication bias: the case for an international registry of trials. *Journal of Clinical Oncology*. 4: 1529 - 1541.

The author compared the pooled results of published trials to those registered on a cancer trial registry for two treatments. In one, a treatment effect evident in published trials was not seen in those on a registry and in the other a treatment effect was seen

in both but much less marked in those in the registry. These different results would have significant influence on choice of therapy.

Easterbrook, P.J. Berlin, J.A. Gopalan, R. Matthews, D.R. (1991). Publication bias in clinical research. *Lancet*. **337**: 867 - 72.

Of the 487 research protocols presented to the Oxford REC, positive studies were twice as likely to be published.

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#### Clinical Trial Websites

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EudraCT database	<a href="http://eudract.emea.eu.int">http://eudract.emea.eu.int</a>
IFPMA	<a href="http://www.ifpma.org/clinicaltrials.html">http://www.ifpma.org/clinicaltrials.html</a>
The ABPI site	<a href="https://www.cmrinteract.com/clintrial">https://www.cmrinteract.com/clintrial</a>
The United States Register	<a href="http://www.clinicaltrials.gov/">www.clinicaltrials.gov/</a>
The International ISRCTN Register	<a href="http://www.controlled-trials.com/isrctn/">http://www.controlled-trials.com/isrctn/</a>
GlaxoSmithKline	<a href="http://ctr.gsk.co.uk">http://ctr.gsk.co.uk</a>
AstraZeneca	<a href="http://www.astrazenecaclinicaltrials.com/">www.astrazenecaclinicaltrials.com/</a>
Roche	<a href="http://www.roche-trials.com/">www.roche-trials.com/</a>
Organon	<a href="http://www.organon-trials.com/">www.organon-trials.com/</a>
Novartis	<a href="http://www.novartisclinicaltrials.com/clinicaltrialrepository/public/login.jsp">http://www.novartisclinicaltrials.com/clinicaltrialrepository/public/login.jsp</a>
HTA	<a href="http://www.htai.org/vortal/">http://www.htai.org/vortal/</a>
Development of the European Register of clinical trials on medicines for children	<a href="http://www.dec-net.org/">http://www.dec-net.org/</a>
NHS National Research Register	<a href="http://www.nrr.nhs.uk/default.htm">http://www.nrr.nhs.uk/default.htm</a>
CenterWatch	<a href="http://www.centerwatch.com/cwworld/cwworld.html">http://www.centerwatch.com/cwworld/cwworld.html</a>
Medical Research Council Clinical Trial Unit	<a href="http://www.ctu.mrc.ac.uk/">http://www.ctu.mrc.ac.uk/</a>
Cancer Research UK	<a href="http://www.cancerhelp.org.uk/trials/trials/default.asp">http://www.cancerhelp.org.uk/trials/trials/default.asp</a>
Gene Therapy Clinical Trials Worldwide	<a href="http://www.wiley.co.uk/genetherapy/clinical/">http://www.wiley.co.uk/genetherapy/clinical/</a>
Current Controlled Trials (University of) Birmingham Clinical Trial Unit	<a href="http://www.controlled-trials.com/">http://www.controlled-trials.com/</a> <a href="http://www.bctu.bham.ac.uk/">http://www.bctu.bham.ac.uk/</a>
British Medical Association	<a href="http://www.bma.org.uk/ap.nsf/Content/clinicaltrialuk">http://www.bma.org.uk/ap.nsf/Content/clinicaltrialuk</a>

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## **ANNEX Y**

### **COMPETENCE, CAPACITY AND CONSENT**

#### **1. Summary**

'Fair' consent depends upon the potential research participant being competent (able) to make a decision, and assessment of competence is therefore a key part of recruitment. It is important that those charged with taking consent are able to identify whether a subject is competent to give such 'fair' consent. Evidence of this would help their application.

Current guidance proposes that all should initially be assumed to be capable. The Mental Capacity Act (England and Wales) enshrines this in law.

#### **2. Evidence**

Adamis, D. Martin, F. Treloar, A. Macdonald, D. (2005). Capacity, consent, and selection bias in a study of delirium . *Journal of Medical Ethics*. 31:137 - 143.

In a study investigating delirium, the researchers found that 'informal' testing of capacity seemed to underestimate those who truly lack capacity (assessed by a more formal structured approach), supporting other work that suggests health care practitioners overestimate capacity. Formal assessment resulted in smaller and biased recruitment. This seems to suggest that 'respect for autonomy' is in conflict with a utilitarian approach to research. RECs may need to weigh these two up and come to a balanced decision when considering how subjects should be recruited, although the Mental Capacity Act (England and Wales) may limit practical room for manoeuvre.

#### **3. Guidance**

The legal position

The High Court (England) held that an adult has capacity to consent if:

- he or she can understand and retain the information relevant to the decision in question;
- believe that information;
- weigh that information in the balance to arrive at a choice;

Therefore to demonstrate capacity individuals should be able to:

- understand, when explained in language comprehensible to most, what the medical treatment is, its purpose and nature and why it is being proposed;
- understand its principle benefits, risks and alternatives (in research it is also important for the subject to understand possible LACK of benefits);
- understand in broad terms what will be the consequences of not receiving the proposed treatment;
- retain the information long enough to make an effective decision;
- make a free choice.

Hotopf, M (2005). The assessment of mental capacity. *Clinical Medicine*. 5: 580 - 584.

Under the English Mental Capacity Act 2005 the definition of person lacking capacity is:

If unable:

- to understand information relevant to the decision;
- to retain that information;
- to use or weigh that information;
- to communicate a decision.

and this is deemed to be situation specific.

Under the Act:

- all are **assumed** to have capacity;
- before deciding someone does not have capacity all steps must be made to enhance decision making;
- a rash decision does not define incapacity;

- best interests must always be taken into account.

Proxy decision making is established in law by this act either by prior arrangement or appointment of a deputy.

The author contends that capacity can be reliably assessed.

### **3. Professional guidance**

Law Society and British Medical Association (1995). Assessment of mental capacity: guidance for doctors and lawyers. London.

The authors maintain that assessment of capacity to consent for research should be the same as treatment.

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## **ANNEX Z**

### **RECRUITMENT TO TRIALS**

#### **Does the means of recruitment matter?**

##### **1. Summary**

Interventional studies

For these there seems to be public opinion that they wish the first approach to be from their health care professional. There is little evidence to indicate whether 'opt-in' or 'opt-out' are both acceptable to the public.

**Opt-in** – The subject is asked by their health care professional (HCP) whether they wish to participate, to be contacted by the researcher if they agree.

**or**

**Opt-out** - The subject is asked by their HCP whether they wish to participate, to be contacted by the researcher unless they decline.

Guidance supports the requirement for consent probably to opt in, the law is uncertain.

##### ***Non interventional studies***

There is evidence that a majority would be happy for unconsented note based study. Guidance requires consent if the data are identifiable, the law is uncertain.

Researchers argue consequentially that the requirement for consent to opt in before a researcher approaches a patient introduces bias and reduces recruitment to such levels that results are not generalisable. They maintain therefore that research and consequently health are suffering. They argue the requirement for consent for all health record research is excessive and undermining public health.

## 2. Evidence

Valid research depends on the sample studied being in as many ways as possible a true cross section of the population. Evidence indicates that the method of recruitment can introduce bias.

Junghans, C. Feder, G. Hemingway, H. Timmis, A. Jones, M. (2005). Recruiting patients to medical research: double blind randomised trial of 'opt-in' versus 'opt-out' strategies. *British Medical Journal*. **331**: 940.

The authors conducted this study to evaluate the effect of opt-in compared with opt-out recruitment strategies on response rate and selection bias. 510 patients with angina were studied from two general practices, randomly allocated to an opt-in or opt-out approach for recruitment to an observational prognostic study of patients with angina. Recruitment rate, 38% (96/252) in the opt-in arm and 50% (128/258) in the opt-out arm ( $p = 0.014$ ). Patients in the opt-in arm had fewer risk factors (44% versus 60%;  $p = 0.053$ ), less treatment for angina (69% versus 82%;  $p = 0.010$ ), and less functional impairment (9% versus 20%;  $p = 0.023$ ) than patients in the opt-out arm.

The authors conclude, 'the opt-in approach to participant recruitment, increasingly required by ethics committees, resulted in lower response rates and a biased sample. We propose that the opt-out approach should be the default recruitment strategy for studies with low risk to participants.'

Jousilahti, P. Salomaa, V. Kuulasmaa, K. Niemelä, M. Vartiainen, E. (2005). Total and cause specific mortality among participants and non participants of population based health surveys. *Journal of Epidemiology and Community Health*. **59**: 310 – 315.

Bias and it matters. In this study of 54,372 Finns the mortality was higher in non participants largest difference being in violence and alcohol related deaths. If results from the study of those who opted in were extended to the population, erroneous conclusions would be drawn.

Al-Shahi, R. Vousden, C. Warlow, C. (2005). Bias from requiring explicit consent from all participants in observational research: prospective, population based study. *British Medical Journal*. **331**: 942.

In a study of adults with a brain vascular abnormality the authors found differences between adults who consent to participate in observational records-based research and those who do not, or cannot. They comment, 'blanket requirements for explicit consent for the use of individuals' identifiable data can bias disease registers, epidemiological studies, and health services research.'

Hanna, L.C. Bhopal, R (2006). Opt-in. [Rapid Response] *British Medical Journal*. **333**: 300 - 302.

'Based on our own research experience, we would argue that these factors are particularly relevant to research with ethnic minority populations and that there is the potential for inequity in participation if an opt-in process is mandatory.'

***There is also evidence that recruitment is falling***

Ingelfinger, J.R. Drazen, J.M. (2004). Registry research and medical privacy. *The New England Journal of Medicine*. **350**: 1452 - 1453.

Armstrong, D. Kline-Rogers, E. Jani, S.M. Goldman, E.B. Fang, J. Mukherjee, D. Nallamotheu, B.K. Eagle, K.A. (2005). Potential Impact of the HIPAA privacy rule on data collection in a registry of patients with acute coronary syndrome. *Archives of Internal Medicine*. **165**: 1125-1129.

Busby, A. Ritvanen, A. Dolk, H. Armstrong, N. De Walle, H. Riano-Galan, I. Gatt, M. McDonnell, R. Nelen, V. Stone, D. (2005). Survey of Informed Consent for Registration of Congenital Anomalies in Europe. *British Medical Journal*. **331**: 140 - 141.

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Tu, J.V. Willison, D.J. Silver, F.L. Fang, J. Richards, J.A. Laupacis, A. Kapral, M.K. (2004). Impracticality of informed consent in the registry of the Canadian Stroke network. *New England Journal of Medicine*. **350**: 1414 – 1421.

There is evidence that a majority would accept some unconsented research using health records.

Academy of Medical Sciences (2006). Personal Data for Public Good: using health information in medical research. Last accessed at:

<http://www.acmedsci.ac.uk/images/publication/Personal.pdf>

Barrett, G. Cassell, J.A. Peacock, J.L. Coleman, M.P. (2006). National survey of British public's views on use of identifiable medical data by the National Cancer Registry.

*British Medical Journal.* 332: 1068 – 1072.

Whiteman, D.C. Clutton, C. Hill, D. (2006). Australian public's views on privacy and health research. *British Medical Journal.* 332: 1274.

Peto, J. Fletcher, O. Gilham, C. (2004). Data protection, informed consent, and research. *British Medical Journal.* 328: 1029 – 1030.

Iversen, A.Liddell, K. Fear, N. Hotopf, M. Wessely, S. (2006). Consent confidentiality and the Data Protection Act. *British Medical Journal.* 332: 165 - 169.

### **3. Guidance**

Professional guidance seems to demand that consent is sought from the patient for research, no views are expressed about opt in or opt out.

NHS Code of Confidentiality and the Patient Information Advisory group (PIAG)

General Medical Council (2000). Confidentiality - protecting and providing information. London.

The 'Caldicott Principles'

Political guidance might be seen to be striking a more cautious balance.

Wanless, D. (2004). Securing Good Health for the whole population. Final report. Last accessed at: [http://www.hm-](http://www.hm-treasury.gov.uk/consultations_and_legislation/wanless/consult_wanless04_final.cfm)

[treasury.gov.uk/consultations and legislation/wanless/consult\\_wanless04\\_final.cfm](http://www.hm-treasury.gov.uk/consultations_and_legislation/wanless/consult_wanless04_final.cfm)

The law disagrees with itself. The data commissioner takes a liberal approach

Walley, T. (2006). Using personal health information in medical research. Overzealous interpretation of UK laws is stifling epidemiological research. *British Medical Journal*. 332: 130–131.

Falconer of Thoroton. (2000): *Freedom of information bill (Hansard)*. Column 261-265.

Information Commissioner. (2002). Use and disclosure of health data: guidance on the application of the Data Protection Act 1998.

Boyd, P. (2003). Health research and the Data Protection Act 1998. *Journal of Health Services Research and Policy*. 8(sup 1): S1 - S7.

While the Department of Health, establishing the Patient Information Advisory Group, takes a cautionary approach, on its website the Patient Information Advisory Group /DH write:

‘Patients provide information about themselves in confidence and where information is held in confidence, common law provides no other reliable justification other than informed consent for use of the information in a patient identifiable form.’

Interestingly, outside the UK, there is legislation to ensure 100% registration in disease registers.

Forman, D. Brewster, D. (2006). Protecting the work of UK Cancer Registries. *British Medical Journal*. [Rapid response].20 May 2006. Last accessed at: <http://bmj.bmjournals.com/cgi/eletters/332/7549/1068>.

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