National Patient Safety Agency

National Research Ethics Service

Information Sheets

&

Consent Forms

Guidance for

Researchers & Reviewers

Please note: We are very conscious that guidance lengthens after every version and we have tried to constrain the length of this document. The main guidance is in pages 1 to 54, not much longer than before. We have had to put in material to cover changes in the law on mental capacity.

Subsequent pages are annexes contain compilations of guidance and published articles on matters arising from guidance. They do not represent NRES' views but are provided to help reviewers and researchers. Comments are very welcome (infosheets@nres.npsa.nhs.uk) .

March 2011

Contents:

1.0 Introduction

It is clear that the public recognises the benefits of medical and health care research and wishes it to continue (Annex 1). 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 base their choice (Annex 2). Empirical evidence indicates that, with occasional exceptions, they themselves want to choose (or at least be involved in the choice) whether to participate once the study has been explained to them (Annex 3). There is evidence, however, that participants' understanding can be limited (Annex 4) hence our emphasis upon designing appropriate processes and information to help them decide.

Researchers therefore need to provide information before seeking consent. This is a central theme in modern research ethics. There may be times when circumstances limit the immediate provision of information and some times when consent (and providing information) is impossible but this must be carefully argued (Annex 5, Annex 6). There are *rare* occasions where withholding information may be acceptable.

2.0 The purpose of this guide

We provide this document to guide researchers and reviewers alike. We have invited and accommodated electronic comment and held regional meetings to gather views.

There may be times when variation will be necessary to provide clearer, more appropriate information. Where researches do deviate from this template, it would be helpful to explain this to the committee. We do not wish to hinder improvement and are very keen to collect examples from researchers and reviewers.

Please email such examples to: infosheets@nres.npsa.nhs.uk .

3.0 Involving public and 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 7), although we recognise that this may not always be possible or appropriate (small scale research or short projects). We advise researchers to be prepared to explain their methods of consultation and engagement to the committee. We also advise RECs to give appropriate weight to the views of patient groups or potential participants that have been consulted.

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

Providing an information sheet is just one part of seeking the consent of participants and the REC will wish to consider the whole process. RECs increasingly wish to reassure themselves of the competence of those who will be seeking consent and we advise researchers to consider how this can be demonstrated.

It is important that the person seeking consent spends time going through written information and should *not* simply give it to the participant to read on his or her own and then return to ask questions. Available evidence indicates discussion is the most effective way to ensure consent is "informed". This should be outlined at the top of the information sheet, perhaps suggesting how long it may take. The onus is on the researcher to ensure the study is explained to the participant.

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 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/rec-community/guidance/#InformedConsent)

This document will be the subject of further 'Use, Comment and Revision'. If you wish, please send comments to infosheets@nres.npsa.nhs.uk .

Supplementary information and references are provided in the separate annexes, which are referenced in the text. 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@nres.npsa.nhs.uk.

5.0 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.

If you make changes, responding to an REC, it would help if these are highlighted, possibly listed at the beginning with an explanation for each.

5.1 Adults

5.1.1 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. You may therefore wish to explain to a potential subject that it is important to take time to read the information sheet *with the researcher obtaining consent* and it is just as important then to have time for questions. Evidence that is available suggests that discussion and questioning are the most effective means of providing information.

5.1.2 One size will not fit all

The level of detail should be appropriate to the nature and detail of the study. 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 less than minimal risk are likely to need a much shorter information sheet and you will not need to complete all sections (for example the explanation of a questionnaire study may be summarised on the front of the questionnaire itself and completion of the questionnaire regarded as consent). At the other end of the spectrum, 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' (Annex 8). We recommend that, where possible, the sequence of subheadings is used, omitting those that are not appropriate to the research. Where researches *do* deviate from this, it would be helpful to explain this to the committee.

5.1.3 Length

There is concern that information sheets are becoming longer and longer and also more complex. However, length does not always mean incomprehensibility. Careful layout can make a difference.

Where appropriate, the information sheet could be divided into two parts:

Part 1 should provide information on the essential elements of the study (it could start with your answer to A6(i) as a summary), then more details, the condition or treatment

under study, the voluntary nature of involvement, what will happen during and after the study, what treatment may be withheld, the participant's responsibilities; the potential risks, inconvenience or restrictions balanced against any possible benefits and the alternative(s). This should allow the participant to decide whether the study is of interest 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 for a short study and for a simple questionnaire study, sufficient information may be provided on the front of the questionnaire.

If it is a lengthy document then a study summary (possibly your answer to question A6(i)), 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 that the potential participant (if you include a summary) reads the full information sheet before considering consent.

5.1.4 Language/ writing style

The information sheet is best written as an invitation (the use of 'we' may help). Use the active tense and avoid the passive. Write it in simple, non-technical terms that a lay person will understand easily (Annex 9). 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.

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.

It will aid your design and application if you have asked for comments from those who might be recruited or lay people (Annex 7) or conducted 'user testing'. This, in itself, does not require REC review.

There are many ways to assess readability.

Calculate the Flesch Reading Ease score or Fog Score, or an equivalent and think how you might improve it.

The "Fog Factor".

Count the words and sentences then divide the words by the sentences

Count the long words (more than two syllables)

Divide the long words by total words, and multiply by 100

Add the two scores together and multiply by 0.4 to give the fog index

Example Fog Scores

- A newspaper advertisement 4
- A popular novel 8
- A report on information technology 20

Others scores (SMOG) could also be used

The Royal National Institute for the Blind provides guidance ("See it right" Clear Print Guidelines) for clarity.

The Plain English Society can provide guidance or assessment www.plainenglish.co.uk .

User testing is another means of helping participants find and understand information. See the Leeds University Testing Organisation – http://www.luto.co.uk .

If you are consenting people who cannot read, we would suggest the Information Sheet is still used but read to the recruit as a "script".

5.1.5 Presentation

Consider the appropriate page size – it may be that A5, or another paper-size and layout would be more suitable.

For the first page, use headed paper of the hospital/institution where the research is being carried out. Charity or patient group logos etc may also be used to indicate they have endorsed the project. 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 have a date in the header/footer to ensure the most recent is used, and numbered pages.

5.1.6 Further guidance for participants (Annex 10)

There is much material to help potential participants find out about research and decide if they wish to participate. We suggest you look through this to see what might be of help, checking its relevance (and that any specified website is still accessible).

5.1.7 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 between research and clinical staff.

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

5.2 Children (Annexes 11, 12, 13, 14, 15, 16)

This section outlines some points to consider when designing information sheet for children. These notes should be considered together with the points outlined in the adult section.

5.2.1 Important points to consider

Be clear whether you are you seeking *consent* or *assent* and, if in doubt, seek guidance (Annex 13). Consent requires a full explanation of the study. Assent (seeking the child's agreement) requires a clear explanation (comprehensible rather than comprehensive) as consent will be sought from the parent.

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) – the value of this is uncertain and written information may be pointless. Parents will obviously need to provide consent.

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.

5.2.2 Consent

Arrangements will vary according to the type of study proposed, ethical considerations and applicable law (Annex 13).

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 (under 16), but children should also be asked for their assent, if appropriate.

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.

6.0 Guidance for design of information sheets for competent adults

6.1 Part 1 of the information sheet

This should allow the participant to decide whether they wish to read and discuss it further. It should provide clear information on the essential elements of the specific study: 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 alternatives.

6.1.1 Document heading

We recommend the document is headed 'Patient Information Sheet', 'Participant Information Sheet' or 'Information about the research'.

6.1.2 Study title

Ask yourself: "Does this explain the study in simple English?"

One consistent title should appear on all the documents and be comprehensible 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.

6.1.3 Invitation paragraph

The invitation is to ask the potential participant to consider the study and then decide whether to take part. Both must be clearly explained. The following is an example:

> *We would like to invite you to take part in our research study. Before you decide we would like you to understand why the research is being done and what it would involve for you.* ***One of our team will go through the information sheet with you and answer any questions you have.*** *We'd suggest this should take about XX minutes*
>
> *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.*

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

6.1.4 What is the purpose of the study?

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

It is entirely reasonable for projects to be primarily educational. This purpose should be made clear.

6.1.5 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 or recruited and how many others will be in the study.

6.1.6 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 to join the study. We will describe the study and go through this information sheet. If you agree to take part, we will then ask you to sign a consent form. 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 possible implications of withdrawal, this should be given in Part 2.

6.1.7 What will happen to me if I take part?

To answer this question, we suggest you try to 'put yourself in the subject's shoes'. It should be clear which procedures are over and above those involved in standard diagnosis, treatment or management while it is also essential to explain whether any normal treatment will be withheld for all or part of the study.

This section should include:

- how long the participant will be involved in the research;
- how long the research will last (if this is different);
- if and how often they will need to meet a researcher, visit a clinic or their GP;

- 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.

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

You should inform the participant if your study will involve video/audio-taping or photography. Specific consent will be needed if published material identifies the subject.

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

Randomised Trial (Annex 17)

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.)

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.

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).

6.1.8 Expenses and payments (Annex 18)

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

6.1.9 What will I have to do?

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

For medical studies you should include a short description of the drug, device or procedure and give the stage of development. 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 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.

6.1.10 What are the alternatives for diagnosis or treatment?

You should explain other possible treatments in therapeutic research, 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.

6.1.11 What are the possible disadvantages and risks of taking part (Annex 19)?

Risk of the disease/condition/illness and the risk of research should be carefully separated. Below we consider the risk of participation itself.

Any risks, discomfort or inconvenience should be outlined. However, explanation of risk is 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 20).

For example:-

"Before participating you should consider if this will affect any insurance you have and seek advice if necessary"

A separate section on issues in genetic research is given in Annex 21. Guidance from the appropriate authority may be needed.

6.1.12 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 Conference 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.

6.1.13 Radiation and the Ionising Radiation (Medical Exposure) Regulations – (IRMER)) (Annex 22)

If the ionising radiation is part of the research study, then information must be given to the participant on any radiation involved and dosage (whether part of standard care or the research protocol), in everyday terms that they can understand.

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.

6.1.14 Harm to the unborn child: therapeutic studies (Annex 23)

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.

6.1.15 What are the possible benefits of taking part? (Annex 24)

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

> *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.

6.1.16 What happens when the research study stops (Annex 25)?

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.

6.1.17 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.*

6.1.18 Will my taking part in the study be kept confidential (Annex 26)?

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 1.

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.

6.2 Part 2 of the information sheet

6.2.1 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 agreement outlining the discussion.

OR

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.

OR

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

6.2.2 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. 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.

6.2.3 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* [insert details eg NHS Complaints Procedure or Private Institutional arrangements]. *Details can be obtained from* [insert details]

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.

6.2.4 Will my taking part in this study be kept confidential (Annex 26)?

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 Caldecott principles and/or appropriate legislation.

The participant should be told:

- how their data will be collected;
- that it will be stored securely, giving the custodian and level of identifiably (e.g. coded, anonymous, etc.);
- 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.

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

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 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 law in the UK but the company will take all reasonable steps to protect your privacy.

6.2.5 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 for this. You should explain what information will be exchanged. There may be circumstances in which informing the GP may not be necessary, acceptable or possible.

6.2.6 What will happen to any samples I give (Annex 27)?

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.

If there is a any possibility that samples may be used in future research, we strongly advise prospective consent is obtained.

6.2.7 Will any genetic tests be done (Annex 21)?

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.

6.2.8 What will happen to the results of the research study (Annex 28)?

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.

6.2.9 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 and has *any* conflicts of interests. These must be declared to the REC and participant. 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.*

6.2.10 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 interests. 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) and the information sheet should state that the participant will be given a copy and a signed consent form to keep.

6.2.11 Further information and contact details

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), should be given and clearly displayed.

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

6.3 The Consent Form

The example of the consent form given below 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.

(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 taking consent	Date	Signature

When completed: 1 for participant; 1 for researcher site file; 1 (original) to be kept in medical notes.

7.0 Guidance for design of information sheets for children/young people

(Annexes 11-16)

7.1 Information sheets for children / young people aged 11 to 15 (as a guide)

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

7.2 Part 1 of the information sheet

7.2.1 Study title

Can the title be understood by a child? If not, give a short title that is easily understood.

7.2.2 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 join 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 to your family, friends, doctor or nurse if you want to.*

7.2.3 Why are we doing this research?

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

7.2.4 What is the medicine, device or procedure that is being tested?

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

7.2.5 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 [condition]. *3000 young people have already helped test this medicine and this project will involve a further 5000 from seven countries.*

7.2.6 Do I have to take part?

You should explain that taking part is voluntary. You could say

No. It is up to you. We will ask you for your consent / assent [use the appropriate word] *and then ask if you would sign a form (if applicable). We will give you a copy of this information sheet and your signed form to keep. You are free to stop taking part at <u>any time during the research</u> without giving a reason. If you decide to stop, this will not affect the care you receive.*

7.2.7 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.

7.2.8 What will I be asked to do?

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.

7.2.9 What other medicines could I have instead?

Explain what other treatments are available, and their relative risks and benefits.

7.2.10 What are the possible side effects of the medicines?

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.

7.2.11 Is there anything else to be worried about if I take part?

The issues of pregnancy and pregnancy testing must be handled sensitively. Please see annex 23

If the use of ionising radiation is required as part of the research study, then information must be given to the young person on the amount of any radiation involved (whether part of standard care or the research protocol), in terms that they can understand.

7.2.12 What are the possible benefits of taking part?

If there are benefits these can be stated but should not place undue influence. 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.*

7.2.13 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:

3.2 Part 2 of the information sheet

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

7.2.14 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.

7.2.15 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.*

7.2.16 What if there is a problem or something goes wrong?

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

7.2.17 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.

7.2.18 What will happen to any samples I give?

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.

7.2.19 Genetic tests (Only include heading if relevant)

Some guidance is given in Annex 21, but more detailed guidance may be needed.

7.2.20 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.*

7.2.21 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.*

7.3 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.

7.3.1 Study title

This should be in very simple, clear terms.

7.3.2 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* [condition] *better than Medicine Y.*

7.3.3 Why have I been asked to take part?

7.3.4 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.*

7.3.5 Do I have to take part?

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

7.3.6 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.

7.3.7 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.

7.3.8 Will the medicine upset me?

Any side effects need to be explained in simple language.

7.3.9 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.

7.3.10 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.*

7.3.11 What happens when the research stops?

State briefly but clearly what will happen afterwards:

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

7.3.12 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.

7.3.13 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.

7.3.14 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.

7.3.15 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.*

7.3.16 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.

7.4 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.

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:

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.

7.5 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 study is a clinical trial of an investigational medicinal product (CTIMP), a person with parental responsibility should sign a consent form after reading this information sheet, once they are happy with the explanation given. This should be separate from the child's consent or assent form.

Rarely, where a person with parental responsibility is not available or willing to act as legal representative in a CTIMP, another person may be nominated as the legal representative and invited to give consent for the child to participate in the trial. This legal representative may be the child's usual doctor or another person nominated by the health care provider. The information sheet for such legal representatives will be similar to that for parents but modified appropriately.

Informed consent in CTIMPs is governed by Schedule 1 to the Medicines for Human Use (Clinical Trials) Regulations 2004. For further guidance, see the NRES information paper available at http://www.nres.npsa.nhs.uk/rec-community/guidance/#CTD

8.0 Information sheets for adults without capacity

The Adults with Incapacity (Scotland) Act 2000, the Mental Capacity Act 2005 and the Medicines for Human Use (Clinical Trials) Regulations 2004 enshrine the ethical principle that any subject should be helped as far as possible to be involved in the decision to participate, even where they do not have the capacity to give consent for themselves (Annex 29).

Potential subjects who have some capacity of understanding should therefore be provided with information about the research, its risks and benefits. The format and content of the information should reflect their capacity of understanding.

8.1 Clinical Trials of Investigational Medicinal Products (CTIMPs)

The requirements for CTIMPs are governed by Schedule 1 to the Medicines for Human Use (Clinical Trial) Regulations 2004 and apply to the United Kingdom and the investigator must seek informed consent from a legal representative.

The information sheet for the legal representative should be designed using the guidance for information sheets for competent adults given earlier but modified appropriately. The information received by legal representatives should indicate that they are not obliged to undertake the role if they do not wish to do so.

For further guidance on appointment of legal representatives, see the NRES information paper available at

http://www.nres.npsa.nhs.uk/applications/guidance/consent-guidance-and-forms/?entryid62=66934

8.2 Research other than CTIMPs – England and Wales

For research other than CTIMPs taking place in England and Wales, inclusion of adults without capacity is governed by the Mental Capacity Act 2005.

Section 32 of the Act requires the researcher to identify and seek the opinion of a “consultee”. If possible, the researcher should identify a person who has a role in caring for the person who lacks capacity or is interested in that person's welfare but is not doing so for remuneration or acting in a professional capacity (‘personal consultee’). If no personal consultee is available or willing to undertake the role, the researcher may approach a ‘nominated consultee’. For further guidance on appointing consultees, see the guidance published by the Department of Health at:

http://www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsPolicyAndGuidance/DH_083131

The consultee is asked to advise the researcher about the potential participant's wishes and feelings in relation to the project and whether he or she should join the research. This means that they must be willing to do it and able to understand the information provided about the project. The Act does not specify what information is needed but it should be similar to the 'patient/participant information leaflet' that would be given to a person with capacity who was being asked to join a research project.

The researcher will need to explain to the personal consultee that they are being asked to *advise* on whether the person who lacks capacity should take part in the project. For example, they should consider whether the person who lacks capacity would be content to take part or whether doing so might upset them. The consultee must also give their opinion on what the person who lacks capacity's past and present wishes and feelings would have been about taking part in the study.

They are not being asked to provide *consent* and if they do not wish to do so they should be under no pressure.

8.3 Research other than CTIMPs – Scotland

Research other than CTIMPs taking place in Scotland is governed by Section 51 of the Adults with Incapacity (Scotland) Act 2000.

The researcher must seek informed consent from a guardian or welfare attorney who has power to consent to the adult's participation in research or, if there is no such person, from the adult's nearest relative.

The information sheet for the guardian, welfare attorney or nearest relative should be designed using the guidance for information sheets for competent adults given earlier but modified appropriately.

8.4 Research other than CTIMPs – Northern Ireland

Research other than CTIMPs taking place in Northern Ireland is governed at present by the common law. The Northern Ireland Government plans to introduce legislation on mental capacity during 2009 in response to the Bamford Review of Mental Health and Learning Disabilty.

At present the guidance for researchers in Northern Ireland is to seek informed *assent* from a close relative or friend of an adult lacking capacity to consent.

The information sheet for close relatives or friends should be designed using the guidance for information sheets for competent adults but modified appropriately.

Please note that in non-CTIMP research taking place in more than one jurisdiction, i.e. Scotland, Northern Ireland and England/Wales, separate documentation will be required for research sites in each jurisdiction.

We provide paragraphs that will be need to be chosen according to which statutory provisions apply.

- Studies under the Mental Capacity Act in England or Wales

  In these he or she is being asked to give *advice* NOT *consent.*

- Studies other than CTIMPs under the common law in Northern Ireland
  In these he or she is being asked to give *assent*.

- CTIMPs anywhere in the UK or other research in Scotland
  In these he or she is being asked to give *consent*

8.5 At Recruitment

Studies under the Mental Capacity Act (England) (In these he or she is being asked to give *advice* rather than *consent*):

> *"We believe* [participant] *is unable to decide for him/herself whether he/she wants to join this study, so we are asking you to advise whether you feel he / she would have wanted to take part."*
>
> *"We ask you to consider the following information about the study and what you know of his/her wishes and feelings about research. We would like to know whether or not you feel he/she would have agreed to join the study, if he/she had been able to decide."*
>
> *"If you feel unable to give advice about this, please say so."*

CTIMPs (i.e. trials under the EU Clinical Trials Directive) anywhere in the UK or other research in Scotland: (In these he or she *is* being asked to give *consent*).

> *"We believe [participant] is unable to decide for him/herself whether he/she should take part in this study. We are therefore asking you to give your consent if you feel he / she should take part.*
>
> *We ask you to consider the following information about the study, including its risks, inconveniences and benefits, and let us know whether or not he/she should take part.*

You may wish to take account of his/her wishes and feelings about research and whether you feel he/she would have agreed to join the study, had he/she been able to make a decision for him/herself.

"If you feel unable to decide whether or not to give consent, please say so."

8.6 At Recovery (if applicable)

Studies under the Mental Capacity Act or non-CTIMPs in Northern Ireland:

If the research participant recovers capacity, their consent to continue in the study should be sought.

"When you became ill, we felt you were unable to say whether or not you should join a study we are conducting. We asked … for his /her advice.

Now you are recovering, we want to ask if you would agree to continue in the study. You are free to withdraw from the study if you wish to."

For studies involving clinical interventions it may be appropriate to add:

"If you decide to withdraw, your doctors will discuss alternative treatment or care provision with you."

8.6.1 At Recovery (if applicable): CTIMPs anywhere in the UK or other research in Scotland:

If consent has already been given by another appropriate person, this consent remains valid in law even if the participant recovers capacity. However, it is good practice to inform the participant about the study and take account of their wishes in deciding whether or not they should continue in the study.

"When you became ill, we felt you were unable to decide for yourself whether or not you should take part in a study we are conducting. We asked … to give consent on your behalf.

Now you are recovering, we want to ask if you wish to continue in the study.

> *You are free to withdraw from the study if you wish to."*

For studies involving clinical interventions it may be appropriate to add:

> *" If you decide to withdraw, your doctors will discuss alternative treatment or care provision with you."*

You will need to say what will happen to any tissue or data collected so far.

8.7 A possible template for a consultee information sheet in research conducted under the Mental Capacity Act

[Study Title]

Information for Consultee

Version ……., Date ……

Introduction

We feel your relative/friend is unable to decide for himself/herself whether to participate in this research.

To help decide if he/she should join the study, we'd like to ask your opinion whether or not they would want to be involved. We'd ask you to consider what you know of their wishes and feelings, and to consider their interests. Please let us know of any advance decisions they may have made about participating in research. These should take precedence.

If you decide your relative/friend would have no objection to taking part we will ask you to read and sign the consultee declaration on the last page of this information leaflet. We'll then give you a copy to keep. We will keep you fully informed during the study so you can let us know if you have any concerns or you think your relative/friend should be withdrawn.

If you decide that your friend/relative would not wish to take part it will not affect the standard of care they receive in any way.

If you are unsure about taking the role of consultee you may seek independent advice.

We will understand if you do not want to take on this responsibility.

The following information is the same as would have been provided to your relative/friend.

Continue with text from participant information sheet edited where necessary to make sense for the consultee.

8.8 A possible template for a consultee declaration form for research conducted under the Mental Capacity Act 2005

(Form to be on headed paper)

Centre Number: Study Number:

Participant Identification Number for this study:

CONSULTEE DECLARATION FORM

Title of Project:

Name of Researcher:

	Please initial box
I [name of consultee] have been consulted about [name of potential participant]'s participation in this research project. I have had the opportunity to ask questions about the study and understand what is involved.	☐
In my opinion he/she would have no objection to taking part in the above study.	☐
I understand that I can request he/she is withdrawn from the study at any time, without giving any reason and without his/her care or legal rights being affected.	☐
I understand that relevant sections of his/her care record and data collected during the study may be looked at by responsible individuals from [name of sponsor and/or host organisation] or from regulatory authorities, where it is relevant to their taking part in this research.	☐
I agree to their GP or other care professional being informed of their participation in the study.	☐

Name of Consultee	Date	Signature

Relationship to participant:

Person undertaking consultation (if different from researcher):

Name	Date	Signature
Researcher	Date	Signature

When completed: 1 (original) to be kept in care record, 1 for consultee; 1 for researcher site file

A possible template for the information sheet for a legal representative in a CTIMP, or the guardian, welfare attorney or adult's nearest relative in other research conducted under the Adults with Incapacity (Scotland) Act 2000

[Study Title]

Information sheet for [legal representative] [guardian, welfare attorney or nearest relative]

Version ……., Date …….

Introduction

We feel that your relative/friend is unable to decide for him/herself whether to participate in this research.

To help decide if he/she should join the study, we would like to ask you to consent on their behalf for them to join the study. We would ask you to set aside your own views and consider their interests and what you feel would be their wishes and feelings. Any advance decisions they may have made and that you are aware of should take precedence.

If you give consent after reading the information we provide, we will ask you to read and sign the Consent Form on the last page of this information leaflet. We'll then give you a copy to keep. We will keep you fully informed during the study so you can let us know if you have any concerns. You can withdraw your relative/friend from the study at any time without giving a reason and without their care being affected.

If you feel you cannot give your consent, it will not affect the standard of care they receive in anyway.

If you are unsure about taking on this role, you may seek independent advice.

We will understand if you do not want to take on this responsibility.

The following information is the same as would have been provided to your relative/friend.

Continue with text from participant information sheet edited where necessary to make sense.

8.9 A possible template for the consent form for a legal representative in a CTIMP, or for the guardian, welfare attorney or adult's nearest relative in other research conducted under the Adults with Incapacity (Scotland) Act 2000

(Form to be on headed paper)

Centre Number:

Study Number:

Participant Identification Number for this study:

CONSENT FORM

Title of Project:

Name of Researcher:

Please initial box

I (name) have been consulted about (name of potential participant)'s participation in this research project. I have had the opportunity to ask questions about the study and understand what is involved and give my consent. ☐

I understand that I can withdraw him/her from the study at any time, without giving any reason and without their care or legal rights being affected. ☐

I understand that relevant sections of his/her care record and data collected during the study may be looked at by responsible individuals from [name of sponsor and/or host organisation] or from regulatory authorities where it is relevant to their taking part in this research. ☐

I agree to their GP or other care professional being informed of their participation in the study.

_____	_____	_____
Name	Date	Signature

Relationship to participant: _____

_____	_____	_____
Person seeking consent (if different from researcher):		
Name	Date	Signature
Researcher	Date	Signature

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

8.10 A possible template for relatives/friends approached to give assent to participation in research other than CTIMPs in Northern Ireland

[Study Title]

Information for Adult's Close Relative or Friend

Version ……., Date ……

Introduction

We feel that your relative/friend is unable to decide for him/herself whether to participate in this research.

To help decide if he/she should join the study, we would like to ask you to say whether you agree they should take part. We would ask you to set aside your own views and consider their interests and what you feel would be their wishes and feelings. Any advance decisions they may have made and that you are aware of should take precedence.

If you give your agreement after reading the information we provide, we will ask you to read and sign the Assent Form on the last page of this information leaflet. We'll then give you a copy to keep. We will keep you fully informed during the study so you can let us know if you have any concerns. You can request that your relative/friend is withdrawn from the study at any time, without giving a reason and without their care being affected.

If you feel you cannot give your agreement, it will not affect the standard of care they receive in anyway.

If you are unsure about taking on this role, you may seek independent advice.

We will understand if you do not want to take on this responsibility.

The following information is the same as would have been provided to your relative/friend.

Continue with text from participant information sheet edited where necessary to make sense.

8.11 A possible template for the assent form for relatives/friends in research other than CTIMPs conducted in Northern Ireland

(Form to be on headed paper)

Centre Number:

Study Number:

Participant Identification Number for this study:

ASSENT FORM

Title of Project:

Name of Researcher:

Please initial box

I (name of close relative or friend) have been consulted about (name of potential participant)'s participation in this research project. I have had the opportunity to ask questions about the study and understand what is involved. I agree to their taking part in this research. ☐

I understand that I can request he/she is withdrawn from the study at any time, without giving any reason and without their care or legal rights being affected. ☐

I understand that relevant sections of his/her care record and data collected during the study may be looked at by responsible individuals from [name of sponsor and/or host organisation] or from regulatory authorities where it is relevant to their taking part in this research. ☐

I agree to their GP or other care professional being informed of their participation in the study.

_____	_____	_____
Name:	Date:	Signature:

Relationship to participant: _____

_____	_____	_____
Person seeking assent: (if different to researcher):		
Name:	Date	Signature
Researcher:	Date:	Signature:

When completed: 1 (original) to be kept in care record, 1 for relative/friend; 1 for researcher site file

8.13 Templates

8.13.1 Giving tissue and blood samples for cancer research

http://www.oncoreuk.org/pages/documents/onCoreUKDonorInformationSheetv208-05-07_001.pdf

or via http://www.eric-on-line.co.uk

9.0 Annex 1: Public perception of research.

How do the public or patients see health care research?

9.1 Summary

Surveys indicate that health care research is not foremost in the minds of the public but when they reflect, they see the benefits of health care research and wish it to continue. Caution is also evident.

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.

The balance is clearly in favour but some concerns about the risks of experimentation, research and the motives of researchers are evident.

9.2 Evidence

9.2.1 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 but:

> *"However, about half of the public also believe that those who participate in clinical trials 'are like guinea pigs' and that they are 'taking a gamble with their health.'"*

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.

Medical Research Council (UK) (2007)The use of personal medical information in research
http://www.mrc.ac.uk/Utilities/Documentrecord/index.htm?d=MRC0038

The qualitative research shows that there is low awareness and understanding of medical research among the general public but workshops indicate that, if the public is informed about what medical research entails, they are generally positive towards it.

9.2.2 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.'

10.0 Annex 2: The Importance of Information.

Why do we emphasize providing information?

10.1 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.

This process is much more than provision of an information sheet and a signature on a consent form and a recent review of evidence indicated (not surprisingly) that talking one–to–one was the most effective way to provide information that was understood. This could be scheduled in (possibly with the length of time this might be expected to take) and explained at the beginning of any printed information.

Subjects need time to ask questions and reflect. There is no exact defined time for this, 24 hours is often quoted but is only a suggestion. Time provided needs to be commensurate with the research, shorter or longer.

Researchers need to explain to RECs how they will do this and it will help their application if they describe their skills and training.

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.

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.

For Clinical Trials of Investigational Medicinal Products the Good Clinical Practice ‘Elements of Informed Consent’ should be consulted (see below).

10.2 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?
- 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.

The GCP elements of Informed Consent are:

- 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.

10.3 Evidence

Flory J Emanuel E 2004 Interventions to Improve Research Participants' Understanding in Informed Consent for Research JAMA 292(13) 1593

> *"Efforts to improve understanding through.. multi-media and enhanced consent forms have had only limited success. Having a study team member or a neutral educator spend more time talking one-to-one to study participants appears to be the most effective way of improving research participants understanding; however further research is needed."*

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.)

10.3.1 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.

10.3.2 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.

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).

11.0 Annex 3: Consent – why should we seek it?

11.1 Summary

Research evidence indicates that the public value their right to choose if they wish to participate in research. Participation based on consent contributes to public trust in research.

It is not, however, a straightforward transaction and there is evidence that potential participants need help in making their decision, often from their health care practitioner.

11.2 Guidance

World Medical Association Declaration of Helsinki, as amended by the 59th WMA General Assembly, Seoul, October 2008

In medical research involving competent human subjects, each potential subject must be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail, and any other relevant aspects of the study. The potential subject must be informed of the right to refuse to participate in the study or to withdraw consent to participate at any time without reprisal. Special attention should be given to the specific information needs of individual potential subjects as well as to the methods used to deliver the information. After ensuring that the potential subject has understood the information, the physician or another appropriately qualified individual must then seek the potential subject's freely-given informed consent, preferably in writing. If the consent cannot be expressed in writing, the non-written consent must be formally documented and witnessed.

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).

11.2.1 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.

11.2.2 Who is the right person to seek consent?

5. 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.

11.2.3 What information should be provided?

6. 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.
7. Consent must be given voluntarily: not under any form of duress or undue influence from health professionals, family or friends.

11.2.4 Does it matter how the patient gives consent?

8. 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.

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 children or adults who are not able to make decisions for themselves. 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 Conference 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.

11.3 Evidence

Medical research Council (UK) (2007)The use of personal medical information in research
http://www.mrc.ac.uk/Utilities/Documentrecord/index.htm?d=MRC0038

In a broad survey conducted by MORI, one conclusion was:

> *"If the public feels in control of their information and its potential uses (i.e. are asked for consent), then they are likely to be more inclined to allow their personal health information to be used for medical research purposes."*

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 physician's discretion. (It is puzzling that while 98% wanted to be involved, 85% wanted the doctor to make the decision, perhaps indicating that for such decisions, patients want and need help).

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 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.

12.0 Annex 4: Do Potential Participants Understand the Information They Are Given?

12.1 Summary

It is clear participants do not always understand what they're agreeing to. Consequently, researchers must provide clear information before they seek consent. Published literature can give guidance.

This difficulty gives further weight to the proposition that researchers should test information sheets with 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.

Key components

- Competence of the researchers
- Competence of the potential participants
- Freedom
- Time
- Discussion
- Opportunity to ask questions

12.2 Evidence of understanding and guidance to improve this

12.2.1 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.

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', unproven and of uncertain 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 did not retain it;
- parents were given partial information to soften the blow;
- parents were given inaccurate information, which reflected the caregiver's 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.

12.2.2 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 physician's, either due to inherent optimism or miscommunication.

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

misunderstanding in that, given equipoise, it's not clear trial entry would benefit the child :

> *'The main reason parents gave for their consent was the hope that trial entry would improve their baby's prospects.'*

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 in decision making.

Flory J Emanuel E 2004 Interventions to Improve Research Participants' Understanding in Informed Consent for Research JAMA 292(13) 1593

> *'Efforts to improve understanding through.. multi-media and enhanced consent forms have had only limited success. Having a study team member or a neutral educator spend more time talking one-to-one to study participants appears to be the most effective way of improving research participants understanding ; however further research is needed.'*

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.

13.0 Annex 5: Consent – its problems

13.1 Summary

There is evidence to indicate that a universal insistence on consent can undermine research, introducing bias and limiting recruitment. Researchers also maintain that the resources required to seek consent may not always be justified. These concerns have particular relevance in epidemiological research where an adequate and representative sample is necessary for any conclusions to have validity.

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.

The legal position is uncertain, varying from country to country and expert advice is needed. Research in England and Wales using identifiable personal health data without consent needs approval from the National Information Governance Board (http://www.nigb.nhs.uk/) for Health and Social Care under Section 251 of the Health and Social Care Act 2008.

13.2 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.

Haynes CL (2007) Legal and ethical considerations in processing patient identifiable data without consent *Journal of Medical Ethics* 33 302

A useful guide to researchers and reviewers to the legal landscape of confidentiality and research, (mainly with reference to England) with an interesting quote at the end:

> *'Although it is not unlawful in itself to process patient identifiable data without patient consent in the absence of Section 60 support (Health and Social Care Act 2001), it does provide the most secure basis in law for processing such data.'* (See above for recent changes)

13.2.1 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, other law 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.

13.2.2 The Legal Position Outside the UK

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.

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.bmjjournals.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).

13.3 Evidence

13.3.1 Consequences of insisting on consent

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

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 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.

13.3.2 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 they 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.

Opt out makes survey of obese children worse than useless 2006 *The Guardian* (UK)

Campaigners argued that the National Childhood Obesity Database was useless as families can opt out, rendering the results biased and unrepresentative of the population.

Junghans C et al (2005) Recruiting patients to medical research: double blind randomised trial 2005 *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 2 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 was 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% *v* 60%; P = 0.053), less treatment for angina (69% *v* 82%; P = 0.010), and less functional impairment (9% *v* 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.'

Angus VC et al 2003 The requirement for prior consent to participate on survey responses: a population based survey in Grampian *BMC Health Service Research* 18 3(1) 21

In this study the authors demonstrate that opt in or a two stage process introduces bias and reduces numbers recruited

13.3.3 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.'*

14.0 Annex 6: Consent in Emergency Research

14.1 Summary

This area is “under-researched” and consequently patients are suffering.

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. Ethical and legal considerations may differ.

Ethical considerations might propose:

14.1.1 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).

14.1.2 Prospective informed consent (PIC) before an emergency event

This may be possible but presents problems.

14.1.3 Consultation of patient groups

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

14.1.4 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.

14.1.5 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.

14.2 Guidance

14.2.1 Ethics

ICH Harmonised Tripartite Guidance for Good Clinical Practice 1997

Where the protocol indicates that prior consent of the trial subject or the subject's legally acceptable representative is not possible (see 4.8.15), the IRB/IEC should determine that the proposed protocol and/or other document(s) adequately addresses

relevant ethical concerns and meets applicable regulatory requirements for such trials (i.e.. in emergency situations). 4.8.15 In emergency situations, when prior consent of the subject is not possible, the consent of the subject's legally acceptable representative, if present, should be requested. When prior consent of the subject is not possible and the subject's legally acceptable representative is not available, enrolment of the subject should require measures described in the protocol and/or elsewhere, with documented approval/favourable opinion by the IRB/IEC, to protect the rights, safety and well-being of the subject and to ensure compliance with applicable regulatory requirements. The subject or the subject's legally acceptable representative should be informed about the trial as soon as possible and consent to continue and other consent as appropriate (see 4.8.10) should be requested

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Research involving subjects who are physically or mentally incapable of giving consent, for example, unconscious patients, may be done only if the physical or mental condition that prevents giving informed consent is a necessary characteristic of the research population. In such circumstances the physician should seek informed consent from the legally authorized representative. If no such representative is available and if the research cannot be delayed, the study may proceed without informed consent provided that the specific reasons for involving subjects with a condition that renders them unable to give informed consent have been stated in the research protocol and the study has been approved by a research ethics committee. Consent to remain in the research should be obtained as soon as possible from the subject or a legally authorized representative.

14.3 Legal considerations

For specific legal considerations, expert advice should be sought.

EU Clinical trials directive

An amendment of the Clinical Trials Regulations (http://www.uk-legislation.hmso.gov.uk/si/si2004/20041031.htm#sch1) permits the inclusion of subjects in a clinical trial without their consent, provided certain conditions are met and the process has the favourable opinion from an REC.

Mental Capacity Act (England and Wales)

> *"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. This would seem to exclude the possibility of research in emergencies without consent or consultation of a relative or legal guardian

14.4 Evidence

14.4.1 The need

Roberts, I. (2005) Trauma care research and the war on uncertainty *BMJ* **331** 1094

The authors argue there is a dearth of trials on trauma care despite its being the second largest cause of death (after HIV/AIDS). Large trials are needed but circumstances mitigate against these. Funding is limited, collaboration in trials not adequately rewarded and the regulatory environment is increasingly complex and demanding. They argue the application of GCP (good clinical practice), suitable for the

development of new drugs, is inappropriate in the necessary trauma studies and a waste of resources.

14.4.2 The public's view of deferred consent

Shakur, H. et al. (2007) Clinical trials in emergency situations *British Medical Journal* **334** 165

The authors describe the UK amendment of the UK Medicines for Human Use (Clinical Trials regulation 2004). They report and refer to CRASH1, a study of corticosteroids in head injury, in which consent could not obviously be sought from the patient. Patients and relatives were informed afterwards. In the case of only 1 of 10,008 patients randomized, was withdrawal requested (by a relative).

14.4.3 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 were given accurate information but did not retain it.
2. Parents were given partial information to soften the blow.
3. Parents were given inaccurate information, which reflected caregivers understanding.

14.4.4 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 an accident and emergency department 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 the 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.

15.0 Annex 7: Involving Patient Groups

15.1 Summary

It is good practice, may improve trial relevance, design and recruitment if researchers involve patient groups. Such studies are more likely to receive a favourable opinion. It will indicate an ethical, patient-centred approach.

If RECs are to reflect or incorporate public and patient opinion they need to look favourably upon (and indeed encourage) studies that have involved the public in their planning.

When dealing with issues such as risk and the level of information required, consultation with such groups will help to ensure it meets the expectations and standards of the community and those who may be recruited.

One of the best ways to assess readability and comprehension is to seek views from the public or patient groups.

15.2 Guidance

Garattini. S., Chalmers, I. Patients and the public deserve big changes in evaluation of drugs *BMJ* 2009;338:b1025

Involve patients in shaping the therapeutic research agenda

> *"The people who have most to lose from industry's dominance in drug evaluation are patients and those caring for them. The changes that are needed to ensure that patients' views are taken into account are unlikely to occur unless there is much greater public awareness of the problems and active engagement of patients and carers*
>
> *One example of a British initiative to highlight unanswered questions about the effects of treatments is the James Lind Alliance (www.lindalliance.org). Drawing on uncertainties harvested for and published in the Database of Uncertainties about the Effects of Treatments (www.library.nhs.uk/duets), the alliance promotes working partnerships and collaborations between patients and clinicians to identify and promote shared priorities for therapeutic research. Asthma was the first health problem it tackled. After considering over 300 uncertainties about the effects of asthma treatments, the alliance selected 10 for referral to research funding organisations. The most*

important concern relates to uncertainties about the possible adverse effects of long term use of drugs for asthma."

Thornton H (1998) Alliance between medical profession and consumers. *British Medical Journal* **316** 148

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 recommend strategies to improve dialogue between activists, participants and researchers:

- develop dialogue through community advisory boards;
- create national ethics committees that can set clear guidelines on national practice and overrule 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.

15.2.1 People in Research

http://www.peopleinresearch.org/

A website of useful resources and guidance

15.2.2 The Involve database

http://www.invo.org.uk/All_Projects.asp

15.2.3 Involve Good practice in active public involvement in research

http://www.invo.org.uk/pdfs/GoodPracticeD3.pdf

Entwistle V et al (1998) Lay perspectives: advantages for health research. *British Medical Journal* **316** 463

The authors discuss lay involvement in research. They found no evidence of benefit provided but arguments in favour were presented within a framework with three focuses

What is the aim of lay involvement and at what stage is it best incorporated?

Who can best contribute the lay perspective?

Which approach will best identify relevant lay views?

Liberati A 1997 Consumer participation in research and health care *British Medical Journal* **315** 499

Describing international efforts to include patients in research priorities and design.

15.3 Evidence

15.3.1 Making research more relevant

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.

Tallon D Chard J (2000) Consumer involvement in research is essential. *British Medical Journal* **320** 380

> *'Our work on osteoarthritis has shown the potential benefit of involving consumers when trying to prioritise the research agenda.*
>
> *In a survey of 112 people with osteoarthritis of the knee we found that a wider range of treatment options was being used by patients than the*

research literature would suggest. From a recent systematic review of the available literature on treatments for osteoarthritis of the knee (930 studies) research on physiotherapy, educational, and complementary treatments was relatively uncommon, at 3.5%, 6.5%, and 5.3% of all studies respectively. Altogether 93 (83%) people responded to our questionnaire, not all of whom answered every question. Fifty two (63%) reported that they had tried physiotherapy, 42 (53%) had received educational interventions, and 18 (23%) used complementary therapies. Thus the literature does not reflect the range of treatments used by patients.'

Calnan M et al (2007) Public assessment of priorities for research: a citizens' jury Lancet **369** 28

A report of discussions and conclusions of a 'Citizen's Jury' in Bristol, UK, to advise on research priorities for primary care and social care, tending to focus on utility

Guarino P et al 2006 Consumer involvement in consent document development *Clinical Trials* **3** 19

In this study the authors could identify no benefit of consumer involvement in developing the information sheet. They discuss these results, and how this is at variance with other reports.

16.0 Annex 8: Consent - The Good Clinical Practice Elements of Informed Consent

16.1 Summary

The principles of International Conference 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;
- that the trial involves research;
- the purpose of the study;
- why the participant has been chosen;
- the voluntary nature of participation and that 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 participant's 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.

17.0 Annex 9: Making information easy to read and understand

17.1 Summary

There is evidence that improvement is possible!

17.2 Guidance

User testing

User testing is a means of helping participants find and understand information. See the Leeds University Testing Organisation – http://www.luto.co.uk .

Plain English Campaign

http://www.plainenglishcampaign.com/crystalmark.html

Gene Therapy Advisory Committee (2000) Guidance on making proposals to conduct Gene Therapy Research on human subjects.
http://www.advisorybodies.doh.gov.uk/genetics/gtac/gtacinf.pdf

Reading ease score of between 80 and 90 is desirable

Example	Score	Percentage who would understand
Very easy comics	97	80-90%
Easy tabloids	95	70-80%
Fairly easy popular	90	60-70%
Standard magazine	90	50-60%
Fairly hard broadsheet	77	30-50%
Difficult academic	31	0-30%
Very hard Scientific	7	-

Berto FD et al Evaluation of the readability of information sheets for healthy volunteers in phase-I trials *Eur J Pharmacol* 56(5) 371

Maybe things are better in Phase 1? The results showed that all information sheets were readable by all volunteers who had at least finished high school. After these preliminary results, some additional linguistic and graphic refinements were adopted in drawing up information sheets. Readability improved to such a degree that all information sheets could be understood by virtually all volunteers.

Boult (2004) Ensuring quality information for patients *Health expectations* **7** 165

Description of the development of an assessment tool

Raynor DK et al A systematic review of quantitative and qualitative research on the role and effectiveness of written information pp55-63 http://www.hta.ac.uk/fullmono/mon1105.pdf

This article discusses information, describes research and gives references for guidance (pp55-63)

Royal College of Paediatrics and Child Health and Barnardos (2001) Accessible leaflets on health for children, young people and their carers

Content and length: Be clear and concise. Use bullet points and indentations for clarity. Question and Answer format is often very useful too. Within a leaflet it is important to confine your information to a few key messages. Make sure you include graphics and illustrations, preferably in colour. One technique which has been found to be very effective is the use of cartoon strips with each frame containing one piece of information but linked by the sequence to the preceding and following frame.

Language: Languages other than English need to be considered in the light of local community/users needs. Use simple words rather than complex ones. Avoid jargon. If medical terms are used, include a simple explanation.

Layout: You should bear in mind that The Disability Discrimination Act requires that information should be made accessible for those with disabilities. For a

leaflet, you should consider the needs of those with a visual impairment. The RNIB produce very good guidelines on how to go about this.

Illustrations: Bear in mind social/age/gender mix.

Checklist for content and presentation:

I have matched my writing to the needs, abilities and age of the reader;

The purpose of the document is clear to the reader;

The document is laid out clearly with headings and a summary of the important points;

My sentences have no more that 15-20 words in them, on average I have used 'I', 'you', 'we' and made the writing more personal;

Where appropriate I have used clear directions;

I have started with a simple outline of the document, perhaps explaining its purpose;

I have liaised with other professionals, teams, departments and agencies and involved users;

The document complies with corporate guidelines, i.e. it uses Trust colours, logos, format, font, style and size. The document is sensitive, in that it will not cause offence to anyone religious belief, political persuasion, racial group, age, marital status or sexual orientation;

I have included contact names/numbers for further information;

I have made sure that people with visual, reading or language difficulties can read the document;

I have tested the document with a sample of those who will use it;

I have included a publication date.

Royal National Institute for the Blind See it Right Clear Print Guidelines

National Reading Campaign SMOGGING
http://www.literacytrust.org.uk/campaign/SMOG.html : A website that will calculate a reading score.

17.3 Evidence

17.3.1 What is a suitable level?

Wilson FL Measuring patients' ability to read and comprehend: a first step in patient education *Nursing Connections* 13 19

In this small study of 25 subjects, mean reported highest school grade was twelfth grade but actual reading level was below 8th grade.

17.3.2 Information sheets are not written of the reading level of the community

Grossman SA (1994) Are informed consent forms that describe clinical oncology research protocols readable by most patients and their families *Journal of Oncology* **12** 2211

Only 6% were at or below the average reading age of the USA public

Gray BH et al 1978 Research involving human subjects *Science* **201** 1094
In this study researchers found that only 7% of consent forms were readable at the "periodical level", an accepted norm.

Loverde 1989 Research consent forms: continued unreadability *Journal of General Internal Medicine* 4 410

Of 100 consent forms, there was evidence that information sheets were becoming longer and more unreadable.

Paasche –Orlow M et al (2003) Readability standards for informed-consent forms a compared with actual readability *New England Journal of Medicine* 348 721

The authors examined their hypothesis that text provided by IRBs in informed-consent forms falls short of their own readability standards.

They conducted a cross-sectional study linking data from several public-use sources, demonstrating that templates and material for information sheets are, on average, 2 years above the average USA adult reading level (Grade 8).

Mader TJ Playe SJ (1997) Emergency medicine research consent form readability assessment *Ann Emerg Med* 29(4) 534

Readability of 88 information sheets was reviewed. Mean readability index was 10 i.e. 10 years of education was required to understand content. Readability worsened as perceived risk of research increased.

18.0 Annex 10: Information Sources

18.1 Summary

Potential participants may require two sorts of information before joining a study. 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.

18.2 Guidance

Useful websites with information about trials

UKCRC *Understanding clinical trials* and *Clinical Trials: what they are and what they're not*
http://www.ukcrc.org/publications/informationbooklets.aspx

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

National Electronic Library for Health
http://www.library.nhs.uk/trials

Institute of Clinical Research
http://www.icr-global.org/

The National Research Register - UK database of research projects
https://portal.nihr.ac.uk/Pages/NRRArchive.aspx

INVOLVE - Promotes public involvement in the NHS.
http://www.invo.org.uk/

Testing Treatments Evans I et al
http://www.jameslindlibrary.org
http://www.jameslindlibrary.org/testing-treatments.html

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

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

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

Information resources about clinical trials
http://www.ukcrc.org/publications/news/clinicaltrialsinformation.aspx

Christie Hospital - Information for research participants
http://www.christie.nhs.uk/research/participants/default.aspx

19.0 Annex 11: Children's research - what are acceptable risks?

19.1 Summary

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. This is another situation where consultation with child and parent groups may help define acceptable risk.

19.2 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

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.'*

19.2.1 USA: Federal Regulations

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

Less than minimal risk - child's assent and parent/guardians permission.

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.

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.

Other than 1, 2, 3 requires consideration by secretary of HHS after consultation with expert panel.

19.2.2 Radiation and children's research

Everard M (2003) Ethical aspects of using radiolabelling in aerosol research Archives of Disease in Childhood 88 659

A discussion of ethical issues that arise when radiation is administered in children's research.

19.2.3 Placebo and children's research

Miller FG et al When do federal regulations allow placebo controlled trials in children *J Pediatr* 142(2) 102

An analysis of the consequences of FDA directives in the USA to promote paediatric trials and the possible increase in placebo controlled trials in this group that will come before IRBs. They particularly look at this exploring the risk benefit profile of studies.

They conclude that the risk/benefit profile of the active and placebo arms are different and should be considered separately.

Placebo trials should only be approved in children if the placebo:

poses minimal risk;

poses greater than minimal risk with a prospect of direct benefit from the placebo that justifies the risk and is at least as favourable as the alternatives;

it poses no greater than minor increase over minimal risk as long as it provides knowledge of vital importance.

There need also to be convincing methodological reasons, for example:

A short-term study with minimal risk from withholding treatment, subjects fully informed, a placebo effect is likely, no licensed therapy or no accepted effective therapy exists.

19.2.4 Legal consideration (England)

Department of Health London Consent why should we seek it?

The lawfulness of medical research on adults or children who lack capacity has never been considered by an English court and therefore no definitive statement of the law can be made.

Where children lack capacity to consent for themselves, parents may give consent for their child to be entered into a trial where the evidence is that the trial therapy may be at least as beneficial to the patient as the standard therapy. It may also be compatible with the welfare principle for a person with parental responsibility to give consent to a research intervention which is not strictly in the best interests of the child but is not against the interests of the child. Such an intervention must involve only minimal risk.

19.3 Evidence

It concerns children.

Wolthers, OD. (2006) Questionnaire on factors influencing children's assent and dissent to non therapeutic research *Journal of Medical Ethics* **32** 292

Of 1281 healthy children aged 6 to 16 asked to participate in a non therapeutic research project, dissenting children were cautious about blood and urine sampling.

As with adults risk acceptance varies.

Shah, S. (2004) How do IRBs apply the Federal risk and benefit standards for paediatric research *Journal of the American Medical Association* **291(4)** 476

Further evidence, albeit in children's research, that perception of risk is hugely variable:

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).

20.0 Annex 12: Children's Research – Children's Views

20.1 Summary

Although the evidence is limited, many of the children interviewed were happy to participate and enjoyed the experience.

Limited literature suggests that parents feel similarly.

20.2 Evidence

Cherrill, J. et al (2006) Clinical trials: the viewpoints of children *Archives of Disease In Childhood* **92** 712

A small study of 30 children - 19 recognised risks but had participated in studies.

Wolthers, OD. (2006) Questionnaire on factors influencing children's assent and dissent to non therapeutic research *Journal of Medical Ethics* **32** 292

Of 1281 healthy children aged 6 to 16 asked to participate in a non-therapeutic research project, virtually all who assented (98% - 638) expressed a desire to help children. Dissenting children were cautious about blood and urine sampling. The authors concluded that assenting children had altruistic and educational motives (they wanted to learn about research).

Johnson, KM. et al (1999) Children in research speak for themselves. *Clinical Pharmacology and Therapeutics* (Abstract presentation)

Of 73 children, 63 completed a questionnaire on their participation in a phase 1 or 2 research project. Just under half expressed altruistic reasons. Virtually all were happy about participating and would do so again.

Fogas, BS. et al (2001) A retrospective study of children's perceptions of participation as clinical research subjects in a minimal risk study *Journal of Developmental and Behavioral Pediatrics* **22(4)** 211

115 of 189 children with ADHD (aged 6 to 19) who took part in a non-therapeutic Ritalin trial (one blood sample) were questioned. 89% realised

participation was voluntary and 97% were satisfied with participation. Reasons given for participation were 39% altruism, 47% self interest. 6% perceived coercion. Like adults a number (37%) thought participation would help them.

20.2.1 Parental views

Burnell, RH. O'Keefe, M. (2004) Asking parents unaskable questions *Lancet* 2004 **364** (Aug 28) 737

Kreicbergs, U. et al (2004) A population nationwide study of parents' perceptions of a questionnaire on their child's death due to cancer *Lancet* **364** 787

A proposed study in Sweden to ascertain the views of parent whose child had recently died of cancer was denied by an REC but a pilot study was agreed to assess harm and benefit. 95% found the study valuable. The study therefore was instituted. 99% found it valuable, 68% were positively affected, 28% negatively affected - 10 (2%) very much.

21.0 Annex 13: Children's Research

When should the child's consent be sought?

21.1 Summary

A research participant's safety and autonomy are protected by their informed consent. For research involving children this obviously presents a problem, consent depends upon the capacity to provide it and as this develops during childhood, researchers and reviewers face the question: "When can a child provide meaningful, informed consent; and when, alternatively, should we seek consent or permission from a proxy, competent major, such as a parent?"

If the study is a clinical trial of an investigational medicinal product, conducted under the Clinical Trials regulations, the law is clear. Regardless of ethical considerations, the parent's or guardians' consent must be sought for any child under the age of 16.

Otherwise the "August Bodies" such as the WHO, WMA or MRC that have considered this issue are deliberately vague, ultimately leaving the decision to researchers and reviewers. Research evidence suggests that most children can understand details of a project by the age of 10 years but are not competent to make a decision until at least 11 and it is only by 11 to 14 they also have adequate 'voluntariness', which suggests we should only seek consent from children over 14.

Although it can provide guidance, this evidence has limitations and must be used cautiously. Given the uncertainty and the views of some who argue that it is impossible to provide definitive ages, careful deliberation by researcher and REC is important and the moral obligation of researchers to assured themselves that what they undertake is ethical, whether or not the child or parent consents, is crucial to their safety.

However, ethical practice is that we tell children what we propose to do, even if we do not seek their consent but, in these circumstances, we provide information to comfort the child, on the principle that if we know what is to happen, it is in some way less frightening. We seek their assent or agreement. Kodisch suggests:

'One helpful approach…may be to separate the educational from the authorisation component of assent' (*Ethics and Research with Children* O.U.P. p16)

If we accept this, we free ourselves from the dominant legal dictat that information must be complete and can concentrate on making it understandable. Information for children in these cases can be comprehensible rather than comprehensive.

21.2 Guidance

21.2.1 Principles to guide research involving children

Royal College of Paediatrics and Child Health (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:

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.

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;

> *In the absence of law… the Gillick principles ('children can consent if they have "sufficient understanding and intelligence to understand what is proposed") might reasonably be applied*

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.

United Nations Convention on the Rights of the Child 1989

This demands that we give:

'due weight in accordance with the age and maturity of the child',

World Medical Association. Declaration of Helsinki 2000
http://www.wma.net/e/policy/b3.htm

This states consent should be sought:

'When a subject is deemed legally competent',

European Union Clinical Trials Directive 2001.
http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=CELEX:32001L0020:EN:HTML

This uses the words:

' according to its capacity of understanding'

But demands parental consent if under 16 years of age.

Using Gillick v Wisbech and W. Norfolk AHA 1984 1 all ER it is proposed that consent should be sought from children when:

'children have "sufficient understanding and intelligence to understand what is proposed''

21.2.2 Legal consideration

Department of Health, London, Consent: why should we seek it?

The lawfulness of medical research on adults or children who lack capacity has never been considered by an English court and therefore no definitive statement of the law can be made.

Where children lack capacity to consent for themselves, parents may give consent for their child to be entered into a trial where the evidence is that the trial therapy may be at least as beneficial to the patient as the standard therapy. It may also be compatible with the welfare principle for a person with parental responsibility to give consent to a research intervention which is not strictly in the best interests of the child, but is not against the interests of the child. Such an intervention must involve only minimal risk.

21.3 Evidence

21.3.1 Do children understand the proposal?

Susman, EJ. et al. Participation in biomedical research the consent process as viewed by children, adolescents and physicians. *J Pediatr* 1992 **121(4)** 547

Susman *et al* assessed knowledge of the "elements of informed consent" in 44 subjects aged from 7 to 20, concluding that chronological age was not related to knowledge of the elements of informed consent and that comprehension was similar in 7 year olds and adults.

Tait, AR. Voepel-Lewis, T. Malviya, S. 2003 Do they understand? (part II): Assent of children in clinical anesthesia and surgery research 2003 *Anaesthesiology* **98** 609-614

Tait *et al* found a trend to suggest their 7 to 11 and 11 to 15 year olds recruited to anaesthesia research did not fully understand study purpose but this didn't reach statistical significance.

Lewis, CE. et al. Informed consent by children and participation in an influenza vaccine trial. *American Journal of Public Health* 1978 **68** 1079

Lewis *et al* studied the understanding of 213 children aged 6 to 9 years when recruiting for a vaccine trial. Their data come from group discussions in class and they found that all groups bar one, (all of 6 year olds), “elicited the relevant information on the details of the trial and the associated risks and benefits”.

Ondrusek, N. et al. Empirical examination of the ability of children to consent to clinical research. *Journal of Medical Ethics* 1998 **24** 158

Ondrusek *et al*, studying a smaller group of 18 children aged 5 to 18, puts the divide at an older age, concluding that it was only children of 9 and over who could understand a research proposal.

Burke, TM. et al. Children’s understanding of the risks and benefits associated with research. *Journal of Medical Ethics* 2005 **31** 715

Burke *et al* studied the understanding and assessment of risks and benefits of two proposed operations to fix a fractured leg (14). They enrolled 251 6 to 15 year old children and 237 adults. Like Susman, they found no age differences when they analysed their data on the understanding of the proposed procedures.

Hurley, JC., Underwood, MK. Children’s understanding of their research rights before and after debriefing: informed assent, confidentiality, and stopping participation *Child Development* 2002 **73(1)** 132

Hurley and Underwood’s study put the age of comprehension slightly later. They studied 178 children, all of whom showed limited understanding of goals of the research. Under the age of 10 all had limited comprehension of the concept of confidentiality.

Weithorn, LA., Campbell, SB. The competency of children and adolescents to make informed treatment decisions. *Child Development* 1982 **53** 1589

Weithorn and Campbell put comprehension at an even later age. Their data indicated that 9 year olds appeared less able to understand a treatment proposal and it was only 14 years olds who approached adult comprehension.

Alderson, P., Sutcliffe, K., Curtis, K. Children's competence to consent to medical treatment *Hastings Center Report* 2006 **36 no 6** 25-34

In contrast, Alderson *et al*, in a descriptive study of 24 children with insulin-dependent diabetes, maintained that children even aged 3 could understand treatment decisions.

21.3.2 Can children be relied upon to make a wise choice?

Weithorn, LA., Campbell, SB. The competency of children and adolescents to make informed treatment decisions. *Child Development* 1982 **53** 1589

Weithorn *et al* refer to other work which provides (legal) tests of competency into

evidence of choice – expression of a preference;

reasonableness of outcome – the choice matches that that a reasonable person might make;

rational reasons – the demonstration of reasoning or logic;

understanding (both comprehension and appreciation) of risks, benefit and alternatives.

Her study demonstrated that the 9 year olds made choices (1) and these appeared to be reasonable (2) but had poorer reasoning (3) and understanding (4).

> *"Younger minors appeared less competent than adults according to the standards of competency requiring understanding and rational, reasonable process. Yet according to the standards of evidence of choice and reasonable outcome, even these younger minors appeared competent … despite poorer understanding and failure to consider fully many critical elements of disclosed information the 9 year olds tended to express clear and sensible treatment preferences similar to the adults."*

Burke, TM. et al. Children's understanding of the risks and benefits associated with research. *Journal of Medical Ethics* 2005 **31** 715

We can see the same pattern in Burke *et al*'s work (14). While the authors argue that there were no age related differences in the assessment of risks and benefits, it seemed the younger groups preferred a plaster cast (rather than operative fixation) even when this was not deemed to be the "reasonable option".

Tait, AR., Voepel-Lewis, T., Malviya, S. 2003 Do they understand? (part II): Assent of children in clinical anesthesia and surgery research 2003 *Anaesthesiology* **98** 609-614

Tait *et al* found 7 to 15 year olds' competence did not match that of their older age group (15 to 18). They had a poorer understanding of the risks and benefits of the proposed research.

Lewis, C. How adolescents approach decisions over grades 7 to 12 and policy implications 1981 *Child Deveopment* **52** 538-544

Lewis *et al* found an age effect in risk awareness, which we might see as a feature of competency, even in 12 to 18 year old subjects, suggesting that this group did not have the competence of adults.

21.3.3 When can a child's decision be free of undue influence.

Ondrusek, N. et al. Empirical examination of the ability of children to consent to clinical research. *Journal of Medical Ethics* 1998 **24** 158

Ondrusek identified that her younger age group (under 9) were susceptible, not realising they could withdraw from a study. Only two of eight under 10 felt it was acceptable to stop, while 7 of the 9 over 10 were aware of this right.

If they did, she describes that some still felt the researcher would be '"sad" or even "mad"' if they said they wanted to withdraw:

> *"But even amongst those who did state it was permissible to stop, there appears to be a feeling of external influence which might prevent them from actually stopping"*

Susman, EJ. et al. Participation in biomedical research the consent process as viewed by children, adolescents and physicians. *J Pediatr* 1992 **121(4)** 547

Susman found contradictory results. While 70 percent of her 7 to 20 year old subjects knew participation was voluntary, only 40% knew they could withdraw suggesting their understanding of voluntariness was questionable.
Abramovich (19) found 12 to 14 year olds were influenced by maternal advice.

Scherer found parental influence in treatment choices of young adults.

Tait, AR., Voepel-Lewis, T., Malviya, S. 2003 Do they understand? (part II): Assent of children in clinical anesthesia and surgery research 2003 *Anaesthesiology* **98** 609-614

Tait's 7 to 15 year olds had statistically poorer understanding of alternative, the possibility of withdrawing and voluntariness.

22.0 Annex 14: Children, Research and Potential Pregnancy

22.1 Summary

This annex will be mainly relevant to therapeutic research in which treatments are unlicensed or outside accepted standards. Consequently under EU directive and UK law, parents must be involved, in that it is they who must legally provide consent.

Kodisch in *Ethics and Research with Children* (115) argues "an ethical case can be made to exclude teenagers at risk of pregnancy" but the counterargument would be that this excludes a group from the benefits of research.

Researchers in this area need to understand the law

22.2 Guidance

Legal considerations

These vary from country to country and researchers will need to look up appropriate law.

Children and Families: Safer from Sexual Crime The Sexual Offences Act 2003 (England)

http://www.homeoffice.gov.uk/documents/children-safer-fr-sex-crime?view=Binary

> *"The legal age for young people to consent to have sex is still 16, whether they are straight, gay or bisexual.*
>
> *Protecting under 13s The Sexual Offences Act 2003 now makes it clear that sexual activity with a child under 13 is never acceptable, and that – regardless of the circumstances – children of this age can never legally give their consent.*
>
> *Protecting under 16s Children under 16 need extra protection from sexual abuse, and the laws in the Sexual Offences Act carry heavy penalties for these offences The following offences apply where the offender is aged 18 or over. Where sexual activity takes*

place between someone below the age of 18 and someone under 16,there are similar offences but these carry a lower maximum penalty.

It is not intended to prosecute two young people of a similar age for engaging in mutually agreed teenage sexual activity, unless it involves abuse or exploitation"

For researchers, there is little guidance on this and it seems problematic to draft proscriptive guidelines:

Be sensitive to local social beliefs;

Involve paediatricians and chairs of ECs in preliminary discussions if this is a real likelihood;

Respect the young person's autonomy but encourage involvement of the parents;

Be aware that in clinical trials of investigational medicinal products parents of children under 16 legally have to provide consent, and this will include consent to pregnancy testing and discussion of contraception.

22.2.1 Is it necessary to recruit adolescents who could conceive?

The RCPCH guidance is that:

'Research should only be done on children if comparable research on adults could not answer the same question.'

It could be argued that children who could conceive will be very similar in physiology and pharmacology to young adults who could be more easily and ethically recruited and, therefore, it is unnecessary to recruit these children. Others argue that peri-pubertal children do have differing physiology.

22.2.2 Who would be considered at risk of pregnancy?

It would be possible to use an age of menarche based on the community to be studied but this will be a figure such as the age at which more than 3% of children will have gone into puberty. This obviously leaves 3% at risk of possible pregnancy. It may be that each young person around this age needs to be managed individually.

22.2.3 Should the parents be involved?

Risk to the foetus will be confined to studies of medicines (Clinical Trails) and these must follow the EU Clinical Trials Directive which contains a legal stipulation that parents have to give consent. They must therefore be involved in discussions about pregnancy and contraception if these are relevant.

When seeking informed consent from parents, the possibility of pregnancy and appropriate contraception will need to be raised if it's appropriate. It would also be necessary to explain to them that you will have to discuss these matters with their child.

When talking to the child you will need to explain why it's important for her not to become pregnant and appropriate contraception. She also needs to know that these issues would be raised with her parents.

22.2.4 What might be deemed "adequate contraception"?

Condoms or diaphragm would not be regarded as adequate.

Methods such as the, the oral contraceptive pill or patch, the injection, implant, IUD or IUS would be considered adequate and it should be recommended these are used along with condoms to provide "safe sex".

22.2.5 When, and which, pregnancy tests should be performed?

These should be undertaken at the start of the study, and subsequently at the discretion of the subject and researcher, AND if there is possibility of conception.

23.0 Annex 15: Children's Research - the principles

23.1 Summary

Principles are clearly laid out in professional, national and international guidance. By and large, they raise the same issues.

23.2 Guidance

Principles to guide research involving children

Ethical Considerations for Clinical Trials on Medicinal Products Conducted with the Paediatric Population
ec.europa.eu/enterprise/pharmaceuticals/eudralex/vol-10/**ethical_considerations**.pdf

Royal College of Paediatrics and Child Health (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:

1. Has the prospect of benefit.
2. Is well designed and conducted.
3. Does not simply duplicate previous work.
4. Is not undertaken primarily for financial or professional advantage.
5. Involves a statistically appropriate number of subjects.
6. 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 by 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.

24.0 Annex 16: Children's Research – the need

24.1 Summary

Some evidence indicates research involving children is needed, and organisations involved in child health support this view. This view is reflected both in political policy and guidance to RECs in the USA and Europe.

There is evidence that fewer studies are conducted in children and those that are, are of poorer quality.

24.2 Guidance

European commission 2002 Better Medicine for Children
http://dg3.eudra.org/F2/pharmacos/docs/Doc2002/feb/cd_pediatrics_en.pdf

24.2.1 Summary

'Before any adult is treated with a medicine, he or she can be sure that it has been extensively tested to assure that it is safe, effective and of high quality for use in adults. The same may not be true for medicines used in children. It is estimated that over 50% of those used, particularly in specialised medicine, have never actually been studied for use in children. The absence of suitable authorised medicinal products to treat diseases in children which have been both tested and assessed is an issue that has been of concern for some time. As a result existing EU medicines frequently do not include information on safe and effective use in paediatric populations. This in turn leads to the use of unauthorised medicinal products and /or medicines used outside their approved terms "off-label" and may result in significant risks, including lack of efficacy and /or unexpected adverse effects, even death. The issue has been raised by regulators, individual Member States, Members of the European Parliament, by paediatricians, and parents. In December 2000, the European Health Council asked the Commission to take specific action to remedy the problem.'

24.2.2 Conclusion

Similar measures to those already taken in the US are urgently needed for European children. These must take account of the specificities and structure of the Community market and pharmaceutical regulatory system. Achieving the right combination of incentives and regulatory obligations which will ensure that both existing and new medicinal products are suitably adapted for the needs of paediatric populations in the Community in a resource efficient manner is a challenge that must be met in order to ensure the best and safest treatments for our children. The aim of this paper is to outline potential options of addressing this challenge by new pharmaceutical legislation.

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.

European Commission 2006 Ethical considerations for clinical trials performed in children 2006. Recommendations of the ad hoc group for the development of implementing guidelines for Directive 2001/20/EC relating to good clinical practice in the conduct of clinical trials on medicinal products for human use http://ec.europa.eu/enterprise/pharmaceuticals/paediatrics/docs/paeds_ethics_consultation20060929.pdf

To sum up: children are not little adults. Differences in pharmacokinetics and dynamics and in adverse reactions are common in children compared to adults. Growth and maturation processes as well as specific diseases are not found in adults.

Trials are necessary and should aim at progressing the well being and treatment prevention and diagnosis of ill health including in children.

24.3 Evidence

24.3.1 It is not 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.'*

24.3.2 There is a 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

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.

Conroy, S., Choonara, I., Impicciatore, P. et al 2000 Survey of unlicensed drugs and off label drug use in paediatric wards in Europeans countries *BMJ* **320** 79-82

Evidence of widespread use of drugs off license in paediatric practice in Europe

Smyth, RL., Edward,s AD. 2006 A major initiative to improve treatment for children *Archives of Disease in Childhood* **91** 212

There is evidence that fewer studies are conducted in children and those that are, are of poorer quality.

Marchant, J. 2006 Evaluation and outcome of young children with chronic cough *Chest* 2006 **129** 1132

The research reported by these authors show that children and adults with chronic cough, cough for different reasons.

> *'Our findings thus suggest that the highly successful and widely used anatomic pathway of Irwin and colleagues which involves the*

> *investigation and empirical treatment of these three common adult diagnoses (causes of chronic cough in adults) initially, should not be applied to children.'*

If they are, correct diagnosis may be missed and effective treatment delayed.

Campbell, H. et al 1998 A review of randomised controlled trials published in the Archives of Disease in Childhood from 1982 -96. *Archives of Disease in Childhood* **79** 192

The authors argue that the 249 RCTs they identified represented a small number and were of poor quality.

Johnson, TN. (2008) The problems in scaling drug doses to children *Archives of Disease in Childhood* **93** 207

An exploration of methods of scaling drugs for children, looking at accuracy, bias and error concluding that scaling from adult practice should be used only as a last resort.

25.0 Annex 17: Randomisation

25.1 Summary

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

25.2 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 MREC 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.

Snowden, C. et al 1997 Making sense of randomisation. *Social Science and Medicine* **45** 1337

A qualitative study of parental understanding of randomisation in a study of Extra Corporeal Membrane Oxygenation in critically ill neonates, demonstrating a limited understanding.

Robinson EJ,et al 2005. Lay public's understanding of equipoise and randomisation in randomised controlled trials. Health Technol Assess. 2005 Mar;9(8):1-192, iii-iv http://www.hta.ac.uk/execsumm/summ908.htm

Healthy adults read hypothetical scenarios and wrote brief answers on judgments on allocation methods, treatment preferences, the acceptability of random allocation, whether or not individual doctors could be completely unsure about the best treatment; whether or not doctors should reveal treatment preferences under conditions of collective equipoise and how sure experts would be about the best treatment following random allocation vs. doctor/patient choice.

Most participants identified which methods of allocation were random but judged the random allocation methods to be unacceptable in a trial context. A majority of participants judged it unacceptable for a doctor to suggest letting chance decide when uncertain of the best treatment and, in the absence of a justification for random allocation, participants did not recognise scientific benefits of random allocation over normal treatment allocation methods.

Participants doubted the possibility of individual equipoise and saw no scientific benefits of random allocation over doctor/patient choice, suggesting that many potential trial participants may have difficulty understanding and remembering trial information that conforms to current best practice in its descriptions of randomisation and equipoise.

This raises considerable problems for explanation of such studies to the public.

Featherstone K, Donovan JL. Random allocation or allocation at random? Patients' perspectives of participation in a randomised controlled trial. British Medical Journal. 1999 317 :11707.

20 participants from a randomised controlled trial were recruited to explore trial participants' understandings of randomisation.

Interviews used a checklist of topics to encourage participants to describe their experiences. Narratives concerning randomisation were compared to identify

common themes, retaining the context of the discussion to allow detailed interpretation. Most participants recalled and described aspects of randomisation, such as the involvement of chance, comparison, and concealed allocation. Many found the concept of randomisation difficult, however and developed alternative lay explanations to make sense of their experiences. Inaccurate patient information and lay interpretations of common trial terms caused confusion.

The provision of clear and accurate patient information is important, but this alone will not ensure consistent interpretation of concepts such as randomisation. Patients may need to discuss the purposes of randomisation in order to understand them fully enough to give truly informed consent.

Pucci E et al patients' understanding of RCTs depends on their education British Medical Journal 1999 318 875

In a small study these authors demonstrated a relationship between length of schooling and comprehension of aspects of trial design.

26.0 Annex 18: Payments to research subjects

26.1 Summary

Paying research subjects raises such questions as “Does money blind people to risk?”; “Does money persuade people to lie about medical history or side effects?”; “What influence does level of payment have on recruitment?“ and “What is the researchers’ responsibility?” In the limited literature it seems that current scales of remuneration did not blind subjects to risk but it is often reasoned that large rewards may persuade people to act against their best interests.

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

Payment to children (beyond expenses) presents particular problems, both ethically and legally.

	Concept	Comment
Expenses	Payment of expenses only.	• If it attracts anyone, in early phase work, it is likely to attract the altruistic and possibly vulnerable. • Units are often cautious of such offers. • There is no incentive to hide medical information.
Barter	Subjects receive access to health care in return for participation.	
Minimum Wage Payment	Participation is paid at the level of unskilled labour or the minimum wage.	• Egalitarian, “those doing the same job should be paid the same” but likely to exacerbate inequity by recruiting unemployed and low wage earners. • Strictly applied it is inflexible.
Market	Subjects are paid whatever sum is required to ensure the study is completed “the law of supply and demand”.	• Grounded in free market theory, adjusted to other factors (time, inconvenience discomfort). • Likely to exacerbate inequity by recruiting unemployed and low wage earners. Open to the criticism “it’s so they can pay as little as possible”. • Adjustable to meet study deadlines and needs. • Problems defining a starting point and open to the criticism that high rewards MIGHT blind subjects to risk.

Salary Reimbursement	Reimbursement of expenses and salary lost.	• Based on the argument that there should be no financial sacrifice by the research subject. • This model would result in inequity in reward for doing the same job. • It would theoretically spread any burden of research more equally.

26.2 Guidance

Food and Drug Administration (USA) 1998

> *'… requires IRBs to review both the amount of payment and the method and timing of disbursement to assure that neither are coercive or present undue influence'*

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.

EU Clinical trial directive 2001/20/EC

Paragraph 4(d) requires there be no inducement for parents or child. Parents can only be compensated for their time.

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 e.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.

Michael, B. (2001) The price of a research subject *International Medical Journal* **94**

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

26.3 Evidence

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

Dunn, LB., Gordon, NE. 2005 Improving informed consent and enhancing recruitment for research by understanding economic behavior *JAMA* **293(5)** 609

Grady, C. 2001 Money for Research participation does it jeopardize informed consent? *American Journal of Bioethics* **1(2)** 40

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.

Halpern, SD. (2005) Towards evidence based ethics *BMJ* **331** 901

Dunn, LB. et al (2008) Worth the risk? Relationship of incentives to risk and benefit perceptions and willingness to participate in schizophrenia research, *Schizophrenia Bulletin* **10**.1093/schbul/sbn003

These researchers did find a relationship between perceived risk and willingness to participate for greater compensation but they also found a significant group who we might say “wouldn't budge”. Some would take a risk some would not.

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.’*

26.3.1 Financial reward and inequity.

The research burden has fallen on the poor.

Brazier M 2008 Exploitation and enrichment; the paradox of medical experimentation Journal of Medical Ethics 34 180

> *'Modern medicine is built on a long history of medical experimentation. Experiments in the past often exploited more vulnerable patients. Questionable ethics litter the history of medicine. Without such experiments, however, millions of lives would be forfeited. This paper asks whether all the "unethical" experiments of the past were unjustifiable, and do we still exploit the poorer members of the community today? It concludes by wondering if Harris is right in his advocacy of a moral duty to participate in medical research.'*

Denny, C., Grady, C. 2007 Clinical Research with economically disadvantaged populations *J Med Ethics* **33** 382

"This is not something you or I do, This is something the poor do so that the rich can get better drugs" Alan Milstein, lawyer for the Gelsinger family

Does money improve or alter this?

Guinea-pigging: healthy human subjects for drug-safety trials are in demand. But is it a living? *New Yorker* Jan 7 2008

A scathing review of phase 1 research, with appalling examples of fraud, exploitation and misconduct. It focuses particularly on the situation in the USA although it is unrefereed and tending toward anecdote.

27.0 Annex 19: The Consequences of Research – risk and harm

27.1 Summary

Research carries a low risk of harm; however there have been rare catastrophic results, mostly in early drug work (Phase I or II) but later work has risk which is difficult to identify, as separation from treatment effects is problematic. Evidence of serious harm in other research is much more difficult to find and usually outweighed by benefit.

Society might therefore forbid research. While this would reduce research risk, 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, the researcher must assess prior work, assess risk, explain it clearly to potential participants and, most importantly, *work to minimise this risk*. RECs will look at this carefully.

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 patients, a place for user involvement.

27.2 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:

It is important at the outset to discern the patients' fears; no technology or language can replace an empathetic approach.

Recognize risk has 'likelihood' and 'consequence' which both need explanation.

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

- beware of 'single event probability' – subjects cant 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..

2006 Expert Scientific Group report on Phase I trials (UK)
http://www.dh.gov.uk/prod_consum_dh/groups/dh_digitalassets/@dh/@en/documents/digitalasset/dh_073165.pdf

Recommendations drawn up after the incidents in a study of the monoclonal antibody TGN 1412 at the Parexel contract research organisation in London (UK).

27.3 Evidence

27.3.1 History

Bernard, C. (1865) *Introduction to the study of experimental medicine*

> *'It is our duty and right to perform an experiment on man whenever it can save his life … The principle of medical and surgical morality consists in never performing on man an*

experiment which may be harmful in any extent, even though the result may be highly advantageous to science and the health of others.'

27.3.2 Evidence of harm

Beecher, H. (1966) Ethics and clinical research *New England Journal of Medicine* **274** 1354

In this article Henry Beecher went about establishing the need for certain ethical principles to be upheld within the research community. Much of the article is concerned with outlining various cases of medical research that he branded unethical and believed damaged the reputation and morality of medicine. Examples of unethical research in the area of the study of therapy, physiological studies, studies to improve the understanding of disease and the technical study of disease are all given, including one example under the sub heading "bizarre study"!

He dismissed the idea that those pieces of research carried out unethically should be published. This he argued this would encourage further ethical abuses in medical research. Beecher's conclusions are those enshrined in today's research ethics committees practices in reviewing research applications. Beecher's first conclusion is of the paramount importance of informed consent in any research carried out on human subjects. If the requirement of informed consent is not upheld then Beecher suggests that there would be grave moral, sociological and legal implications. Integral to the idea of genuine informed consent is that the subject or his guardian must have a full understanding of what is to be undertaken and that all hazards are made clear. If these are not known, Beecher goes on, this, too, should be stated. The other component to Beecher's so called ethical approach to experimentation on man (the other being fully informed consent), is the need for the presence of an intelligent, informed, conscientious, compassionate, responsible investigator. This he argued is the research subjects' ultimate and most effective protection against exploitation or exposure to risk.

Livingston RB (1975) Progress Report on Survey of Moral and Ethical Aspects of Clinical Investigation (to NIH) *Ethics in Science and Medicine* 2 50

Referring to an experiment in which cancerous cells were injected into debilitated elderly subjects (funded by NIH) it was held that the judgement of the investigator is not sufficient as a basis for reaching a conclusion regarding the ethical and moral set of questions in that relationship.

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 (a molecule known to be hazardous). Jesse Gelsinger suffered from a mild form of an inherited metabolic disorder which questionably didn't need treating, died as a consequence of experimental genetic therapy. He outlined what he felt 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.

27.3.3 Harm in non–drug research

Evans, M. (2002) It doesn't cost anything just to ask, does it? *Journal of Medical Ethics* **28** 41

Of 959 returned questionnaires in a study, 3 concerned the researchers but in only one case could this be really attributed to the research project. In this case the participant was angry she received it while waiting for an outpatient appointment to manage the condition being questionnaired.

Taylor, C. (1991) Stress and cancer surveys: attitudes of participants in a case control study *Journal of Epidemiology and Community Health* **45** 317

The authors sent a questionnaire to participants in a case control interview study of invasive cervical cancer. 90% replied, only 2/226 regretted participation, half found benefit even in this sensitive area of research.

Jacomb, P. et al (1999) Emotional response of participants to a mental health survey *Social Psychiatry and Epidemiology* **34** 80

Respondents to a mental health questionnaire were asked for their feelings about such a study. 5% reported distress 3% depression and 3% were concerned about privacy but 35% reported feeling good about themselves.

The authors concluded that every effort must be made to minimize adverse reaction but a large number felt positive after the questionnaire.

The importance of scientific review

Mclellan F (2001) 1966 and all that – when is a literature search done *Lancet* 2001 358 646

The author explores the failure to identify risks of inhaling hexamethonium, that led to the death of a volunteer in a research project at Johns Hopkins University. Old articles highlighting the danger were missed as they were published before Medline starts (1966). Ways of ensuring a comprehensive literature review are discussed

Chalmers,I 2007 "Regulation of Therapeutic research is compromising the interests of patients" International Journal of Pharmacological Medicine 21(6) 395),

The author argues, giving examples, that inadequate prior review has in the past jeopardised research subjects safety.

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.'*

28.0 Annex 20: Incidental discovery of pathology: how should such incidents be handled?

28.1 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.

Is the risk explained to the participant?

Are consequences outlined (to health and life insurance if an abnormality is found)

Who would review the imaging study?

What is the expectation and risk related to further investigation and management of such findings

Is funding of, and responsibility for, any further necessary tests clear?

28.2 Guidance

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".'*

28.3 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).

29.0 Annex 21: 'Genetic' Research

29.1 Summary

There is evidence that the public is cautions about genetic research but it must be recognised that genetic research is a broad area and consequently the risks of studies under this "umbrella " are very variable, from anonymised or pseudonymised pharmacogenetic, studies exploring the genetic influence on how we handle drugs, where there is little risk of harm, through to specific genetic testing for life threatening conditions (cystic fibrosis, haemachromatosis, Huntingdon's chorea are examples). Research design, information and information sheets therefore need to recognise public concern yet be commensurate. Expert advice should be sought. For gene therapy follow guidance from the Gene Therapy Advisory Committee (http://www.advisorybodies.doh.gov.uk/genetics/gtac)

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.Public perception of “Genetics”

29.2 Public support / genetic ‘exceptionalism’

Stegmayr, B., Asplund, K., 2002 Informed consent for genetic research on blood stored for more than a decade *British Medical Journal* **325** 634

Of 1409 patients approached for their blood to be used in genetic research 10 years after donation, 93% consented provided REC had approved the study, 31 objected (2.2%),64 didn’t reply and 3 provided incomplete answers. The researchers found no great difficulty gaining consent and report no distress caused

McQuillan G et al (2006) Genetic Research and donation of tissue samples. What do potential sample donors in the Swedish general public think? *European Journal of Public Health* **16(4)** 433

The aim of this study was 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. Most respondents (86.0%) would donate a linked blood sample for research purposes. Another 3.0% 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.

Consent for genetic research in a general population: The NHANES experience *Genetics in Medicine* 2003 **5(1)** 35

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% (95% confidence interval 82.4–85.6) of eligible participants consented to have their blood samples included in a national repository for genetic research. In 2000, 85.3% (95% confidence interval 84.0–86.6) 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).

Wang, SS. et al (2001) Public attitudes regarding the donation and storage of blood specimens for genetic research *Community Genetics* **4** 18

Asked in a public survey to respond to the comment "I would be willing to donate blood for research to find genes that affect people's health" using a 1 to 5 scale, 1403 (53%) agreed while 47% disagreed. This would seem to suggest a more cautious public view of genetic research**.**

SCIENCE AND SOCIETY: what scientist and society can learn from each other Worcester RM
http://www.mori.com/pubinfo/rmw/cambridge.pdf

Overwhelmingly, the British public insist that people should always be asked for their permission for their blood or tissues to be used in a genetic test (88%, including 62% who say they ‘strongly agree’). Strong majorities also feel that:

- Parents have a right to ask for their child to be tested for genetic disorders that develop in childhood (78% agree);
- People should be encouraged to be tested in young adulthood for disorders that develop in middle age or later in life (77%);
- Genetic techniques should not be made available to parents so that they can have a baby of the sex they choose (75%) but … Genetic information may be used by parents to decide if children with certain disabling conditions are born;

- Attitudes are split on whether new genetic developments will bring cures for many diseases and whether if others have access to your genetic information they will know too much about you;
- There is also a strong minority (41%) who are concerned that research on human genetics is tampering with nature and is therefore unethical and nearly three in four are undecided if new genetic developments will mean children who are healthier and free from inherited disabilities

30.0 Annex 22: X-Rays and Radiation

30.1 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 which would be proposed in medical research) is harmful. Nevertheless the Health Protection Agency advises caution and proposes that it should be assumed that *any* radiation dose might be a risk, albeit small. It is useful to define *two different effects of radiation* –

Stochastic or chance effects and **Tissue** effects or non-chance or deterministic effects – the latter are dose related.

30.2 Terminology and units

ARSAC - Administration of Radioactive Substances Committee, giving guidelines limiting the amount of isotopes given to patients.

IRMER - The Ionising Radiation (Medical Exposure) Regulations

Becquerels and (Radio)activity -The activity of a radioactive sample is given by the
number of disintegrations occurring in the sample per second. A sample has an activity of 1 MBq (one Megabecquerel) if it is decaying at a rate of 1million disintegrations *I* second . This unit is quite different from the unit of radiation dose, the MSv.

Absorbed dose - energy absorbed per unit mass of tissue in Joules/kg. The unit 1 J/kg, is the Gray (Gy). We modify the basic unit to take account of the different biological effects of different types of radiation and call it the:

Equivalent dose - The unit is the sievert (Sv) or millisievert (mSv)

Equivalent dose = Absorbed dose x biological effect.

We can calculate the radiation dose to each *organ* of the body but it would be much easier to deal with a *single figure combining the different organ sensitivities and giving the overall effect on the body.* Each organ/tissue has a different sensitivity to radiation and is assigned a 'weighting factor' in calculating doses. This is the:

Effective dose also with units of sieverts (Sv or mSv)

Effective dose = Absorbed dose x biological effect + organ sensitivities.

Effective doses allow comparison of different investigations and quantify risk

We can attribute a numerical risk (eg of death by leukaemia) to each Sv of effective dose (1 in 20,000 for each *m*Sv)

Category	**Examination**	**Effective Dose (mSv)**
Simple x-ray	Chest	0.05
Simple x-ray	Skull	0.15
Simple x-ray	Abdomen or pelvis	1
Complex x-ray	IVU	3.5
Complex x-ray	Barium meal	3
Complex x-ray	Barium enema	7
CT	Spiral CT abdomen	4
Nuclear Medicine	Tc-99m Bone scan	3
Nuclear Medicine	F-18 FDG PET scan	10

Calculations have margins of error. If you see on an application that the effective dose is 4.42 mSv, in practice this will mean anything from 3 mSv to 6 mSv

Term for risk	Range of risks	Example causes	Risk Estimate
Negligible	Less than 1:1 million	Point at which risk of cancer from food product is considered to be of concern	1 in 1 million
Minimal	Between 1 in 1 million	Drowning in bath	1 in 600,000
	and	Killed by lightning	1 in 300,000
	1 in 100,000	Pregnancy for mother	1 in 170,000
Very low	Between 1 in 100,000	Anaesthesia (risk from single administration)	1 in 50,000
	and	Commercial aviation from 1000 miles jet travel per year	1 in 30,000
	1 in 10,000	Commuting 2 h per week by train or bus from 40-65 years	1 in 10,000
Low	Between 1 in 10,000	Work in service industry	1 in 6,000
	and	Murder	1 in 3,000
	1 in 1,000	Work in manufacturing industry	1 in 2,500
		Accident at work	1 in 2,000
Moderate	Between 1 in 1,000	Cycling for 300 miles per year for next 30 years (accident)	1 in 1,000
	and	Additional risk of fatal cancer from work with ionising radiation 1 mSv per year from 40-65 years	1 in 800

	1 in 100	Accident on the road	1 in 500
		Living in large city (air pollution)	1 in 160
High	Greater than 1 in 100	Lifetime exposure to background radiation (2.3 mSv per year)	1 in 100
		Pneumonia and influenza	1 in 30
		Smoking 10 cigarettes per day	1 in 5

30.3 Guidance

30.3.1 Approval for research involving ionising radiation

All research involving ionising radiation should be reviewed by a Research Ethics Committee (REC). Under IRMER, research exposures must be approved by one of the following:

An ethics committee recognised under the Clinical Trials Regulations (as well as a number of NHS RECs this includes the Gene Therapy Advisory Committee and some independent committees recognised for the review of Phase 1 trials)

The ethics committee constituted under the Adults with Incapacity (Scotland) Act 2000 (currently this is Scotland A REC)

Any other committee established to advise on the ethics of research investigations into human beings and recognised for that purpose by the Secretary of State, the National Assembly for Wales or Scottish Ministers (in effect this means all NHS RECs and HPSS RECs in Northern Ireland, including all Authorised RECs).

The main REC is responsible for review of all ethical issues in the research, taking account of potential variations in clinical practice at sites. The ethical review must consider any radiation exposure (whether part of standard care or the research protocol), and ensure this is adequately explained to the potential

participant. The main REC will consider whether the additional exposure is ethically acceptable, the risks and burdens involved in relation to the potential benefits and the description of risk in the participant information sheet. Where there are differences between sites in radiation practice in clinical care, the main REC will need to consider whether this affects the ethical opinion.

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.

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.

A favourable ethical opinion does not replace the statutory requirement for exposures to be individually justified by Practitioners at each site under IRMER.

National Radiological Protection Board. (2001). *X-rays how safe are they?* Last accessd at:
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 100,000 to 1 in 1,000,000
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

ight or chest x-ray : 50 mSv

Average annual background 2.5 mSv

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.

30.4 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 (old unit for radiation dose: 1 millirem (a thousandth of 1 rem) = 0.01 mSv) 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.

31.0 Annex 23: Research and Potential Pregnancy

31.1 Summary

If they are to benefit from evidence based care, women need to be included in research. However precautions are required to minimise the possibility of injury to fertility or the foetus. Scientific review must evaluate the risk to women and their unborn child and the committee needs to assure itself that any risks identified are adequately explained to potential participants.

This requires particularly sensitive handling in girls under the age of 16.

Consideration also needs to be given to consequences for male fertility.

31.2 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 foetus. 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 foetus 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:

31.2.1 For women:

Please share this information with your partner if it's appropriate.

The treatment might harm an 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, we will ask you 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.

31.2.2 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.

Royal College of Physicians London 2007 *Guidelines on the practice of ethics committees in medical research with human participants*

> *'A general policy of excluding potentially fertile patients from clinical trials would be unethical'*
>
> *'the possible effects on drugs on sperm in men may also need to be considered'*
>
> *'participants should be encouraged to discuss risk with partners'*

The recommendations discuss appropriate contraception and timing of pregnancy testing

The recommendations include the statement

> *"We consider that there can be legitimate research directed at benefiting the mother where fetal loss can not be excluded"*

although "ethical" might be a better word than "legitimate"

It also discusses appropriate consent and its timing

The Sick Children's Hospital in Toronto *Contraception & Pregnancy Issues in Research Protocols Sick Childrens Hospital REB Guidelines*

This is published guidance from The Sick Children's Hospital in Toronto

Context

Some research protocols mandate adequate contraception and pregnancy testing before recruitment e.g. drug trials, interventional radiology projects. This requirement can lead to the exclusion from the study of patients who are found to be pregnant, or who decline the use of adequate contraception. The circumstances around which this exclusion occurs could have the unintended consequence of constituting a significant breach of privacy and confidentiality.

Principles & Issues

1. There is no intention to exclude subjects of childbearing age. On the contrary, these guidelines are to facilitate their inclusion and avoid the creation of research orphans by protecting their rights.
2. In Ontario, there is no age of consent for testing, treatment or research. Determination of a person's capacity to give valid consent is based on ability to understand the information relevant to participation or non-participation, and ability to appreciate the consequences of that decision.
3. Cultural and religious views on contraception, pregnancy and sexuality can have a profound influence on research subjects and their families. In some cases, such information can result in a woman's safety, or even her life, being at risk. Accordingly, discussion of these subjects with research participants requires the strictest preservation of confidentiality.

Therefore the following are suggested with regard to pregnancy testing and contraception:

Pregnancy Testing

1. Describe provisions for a private interview space to allow the child/adolescent to be able to refuse participation privately if she is, or could be, pregnant, without disclosing her pregnancy or sexual activities to her parents or partner.
2. If pregnancy is being tested for, ensure the inclusion of relevant clinical follow-up in the event of the diagnosis being confirmed e.g. social work involvement, counseling.
3. Describe provisions for the management of the patient if she refuses these services.
4. In long term studies involving young females, ensure that these methodological issues are addressed in a manner that reflects understanding of the changing behaviors of the maturing child.
5. Ensure that consent forms clearly state that the patient may be excluded from the study for reasons which the researcher will not be able to divulge to the parents e.g., There can be a variety of reasons which lead to the exclusion of patients from studies. These reasons will be kept confidential. This is to ensure that the patient who is pregnant, or sexually active and not using appropriate contraception, can be excluded from the study without divulging the reason to the parents (and thereby breaching confidentiality).

Contraception

1. If contraception is being mandated in the study, discuss the acceptability of abstaining from intercourse for the required time.
2. Avoid mandating contraception for patients who are unable to become pregnant due to their individual circumstances e.g. extreme illness or young age.
3. Ensure that the cost implications of mandatory contraception are addressed in the study budget.

31.3 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.

32.0 Annex 24: The Consequences of Research

Possible benefit?

32.1 Summary

Some studies purport to show a benefit if you participate in therapeutic trials even if you receive placebo 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 medicinal study. There does however often appear to be benefit in observational studies where participants feel they can tell their story while someone listens.

32.2 Evidence

Lantos, J. (1999) The benefits of inclusion in a trial *J Pediatr* **134(2)** 130

> *" If clinicians try a new therapy with the idea of studying it carefully, evaluating outcomes, and publishing the results, they are doing research. Research is thought to be risky, and the subjects of the research are thought to be in need of special protection. Therefore an institutional review board (or REC)will review the protocol, the informed consent form will be carefully scrutinized, and the research may be forbidden. If the study is permitted, every adverse event will be carefully documented and scrutinized. If, however, clinicians try the same new therapy without any intention of studying it, it is not research and does not need institutional review board approval, consent may be obtained in a manner governed only by the risk of malpractice litigation, and adverse events may not necessarily be noticed or analyzed. It would seem that the patients in the second situation are at much higher risk than the patients in the first. After all, the physicians in the first situation are carefully evaluating the therapy, whereas the*

physicians in the second situation are using the therapy based on imperfect hunches. "

The author in this editorial goes on to discuss the benefit of being included in a study even if you receive the placebo or standard therapy arm of that study, an observation frequently made by other authors.

Are randomized clinical trials good for us (in the short term)? Evidence for a "trial effect". *Journal of Clinical Epidemiology* **54** 217

The authors conducted a systematic review of the literature to see if there a 'trial effect'. Their caveat was that the quality and quantity of the evidence available is limited and they conclude that the evidence is uncertain but a positive, rather than a negative effect on the outcome of patients is likely

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 newborn 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 which holds 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.

32.2.1 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/Forms/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.

33.0 Annex 25: End of trial arrangements

What should participants expect at the end of a research study?

33.1 Summary

While this is a clear issue for trials of medicines (CTIMPs), consideration needs to be given to any project that evaluates health care delivery or possible treatments. There is continuing debate about the arrangements for subjects and the community once a research project has ended. There is little available evidence as to how society sees the problem. It 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.

Studies will give rise to ethical problems if there is clearly no intention or possibility of the therapy being used in the study population or community. In such a case it would seen that a population is being used as an experimental base for another group or, in other words, a means to someone else's ends. But is research only ethical if treatment is certain to be put into immediate practice?

There is agreement that any participant must understand the arrangements after the study has ended and what will then be available. There is no universal mandate to provide therapy beyond the trial but arrangements must be made clear to a potential participant before consent is sought.

The researcher and reviewer should agree one of 5 options

No therapy available after the trial.

Therapy available to all those in the trial already taking it.

Therapy available to all participants.

Therapy available to patients on a named patient basis with SAE reports.

Drug available on an open label basis for a cohort observational study.

33.1.1 Questions for the REC and Researcher to Consider

Provision of medicine or care after the project

Practical considerations

Who will be funding treatment after the trial?

Their stated agreement is needed if the REC decides that provision of therapy after the trial is an ethical precondition.

Who would carry liability for the medication outside the trial?

Their stated agreement is needed if the REC decides that provision of therapy after the trial is an ethical precondition.

Can the sponsor legally provide the therapy?

If it is unlicensed, this may not be possible. If unlicensed a medicine will need to be as part of a further study, or on a named patient basis.

What are the resource and financial implications of providing treatment and would these jeopardise the trial?

If so, the consequences of NOT doing the trial must be weighed against those of doing the study without further provision of “therapy”.

Will results of the trial be available for use immediately or soon after the subjects finish?

Nowadays this is rarely the case, as studies need analysis, review and publication. They also often need to be repeated to confirm their findings.

Will the results of this study provide unequivocal evidence of effectiveness or efficacy?

In modern care, a single study rarely provides this conclusively (See section 3)

Ethical considerations

Have efforts to provide the therapy been "reasonable and in good faith"?

Explanation to potential participants

Will the subjects understand the arrangements at the end of the trial prior to agreeing to participate?

33.2 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 adds:

> *'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.'*

33.3 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.

Oxman A, Glasziou P Williams JW (2008) What should clinicians do when faced with conflicting recommendations BMJ 337 a2530

34.0 Annex 26: Confidentiality and Use of Personal Data for Research

34.1 Summary

It is crucial to use and store data in ways in which public, patients and participants have trust.

There is widespread concern that some interpretations of law and ethical decisions (particularly in the stipulation that consent must be sought) are unreasonably hindering legitimate research.

Wanless, D. (2004). Securing Good Health for the whole population. Final report. Last accessed at: http://www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsPolicyAndGuidance/DH_4074426

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 is complex but it is important, at the outset, for RECs to understand they are not expected to deliver legal opinion.

34.2 Guidance

34.2.1 Handling data

Department of Health (England and Wales) The 'Caldicott Principles'

1.3 A key recommendation of the Caldicott Committee was that every use or flow of
patient-identifiable information should be regularly justified and routinely tested

against the principles developed in the Caldicott Report.

Principle 1 – Justify the purpose(s) for using confidential information

Principle 2 – Only use it when absolutely necessary

Principle 3 – Use the minimum that is required

Principle 4 – Access should be on a strict need-to-know basis

Principle 5 – Everyone must understand his or her responsibilities

Principle 6 – Understand and comply with the law

MRC Ethics Series: Personal Information in Medical Research Guidance on safeguarding data

1. Modify information as soon as possible so identities are not evident - suggestion of a coding system.
2. Whenever possible recommendation 1 should be the remit of the treating clinical team.
3. Consider all arrangements of data storage and make it commensurate with the consequences of disclosure
4. Members of any team should be under a clear duty of confidentiality, by contract with consequent disciplinary action. Team leaders have a responsibility to ensure all working on a project understand their legal and ethical duties
5. Consider the physical environment and who has access – this should be limited to those who might have a fair / legitimate right.
6. Computers should not be left unattended. Data should be ID and password protected. Passwords must be only used by the individual and should be changed regularly.
7. Avoid long term storage on laptops
8. Data transferred over the internet should be encrypted

34.2.2 Data storage and consent

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.'*

MRC Ethics Series: Personal Information in Medical Research Common Law

> *"In the UK, the confidentiality of personal information is addressed primarily in Common Law . . . anyone who receives information must respect its confidentiality (that is, not disclose it without consent or other strong justification) . . . while Common Law establishes some core principles, it does not specify when confidential information may or may not be disclosed to others in*

> *research or most other activities. Individuals and organisations using confidential information have to take responsibility for deciding what is justified and acceptable on a case by case basis . . . Common Law also recognises that it can be in the public interest for doctors to disclose confidential personal information, and that the nature and scale of disclosure has to be…*
>
> *balanced against the benefits to society . . . there are few court rulings relevant to the sorts of limited disclosures involved in research."*

The legal advice to MRC is that the legality of using confidential information in research without consent could only be judged on a case by case basis, taking into account:

Necessity – were there alternative, practical ways of conducting the study, which would have allowed consent to be obtained?

Sensitivity – how much did the information reveal about the individual and was it particularly likely to lead to worry or distress or damage the doctor-patient relationship?

Importance – was the research well designed and likely to make a significant contribution to knowledge in the area?

Safeguards – was the amount of information disclosed as small as possible? Were all reasonable steps taken to guard against unintended leaks of information and to maintain trust? Was the risk that the study or its findings might cause distress minimised?

Independent review – was the justification for the research reviewed by a Research Ethics Committee?

Expectations – if explicit consent was not possible, were there reasonable efforts to make people involved aware of how medical records were used, so they had an opportunity to raise any special concerns?

Lord Falconer of Thorton. (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.

The research community's views

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.

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.

Metcalfe C (2008) Low risk research using routinely collected identifiable health information without informed consent: encounters with the Patient Information Advisory Group *Journal of Medical Ethics* **34** 37

Haynes C et al (2007) Legal and ethical considerations in processing patient identifiable data without consent. *Journal of Medical Ethics* **33** 302

A useful guide to researchers and reviewers to the legal landscape of confidentiality and research. finishing with a sting in the tail.

34.3 Evidence

34.3.1 Public and researcher's views

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.

Given that in a BMA survey, 93% of respondents agreed with the comment that doctors should not 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 were 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 effects 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 (from over 1000 contacted) 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.

Busby A et al (2005) Survey of informed consent for registration of congenital anomalies in Europe *British Medical Journal* **331** 140

The authors argue that the logistic difficulties of seeking consent for this registry and the tiny documented number of parental refusals together suggest that seeking consent for registering a child with a congenital anomaly may be incommensurate.

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.bmjjournals.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).*

Armstrong D (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

Evidence that the Health and Insurance Portability and Accountability Act in the USA has led to a fall in recruitment to this register and introduction of bias (mirrored in studies in the EU).

35.0 Annex 27: Samples

35.1 Summary

Research using human tissue requires legal consideration. The Human Tissue Authority was set up to regulate the removal, storage, use and disposal of human bodies, organs and tissue for a number of Scheduled Purposes – such as research, transplantation, and education and training – set out in the Human Tissue Act 2004 (HT Act). The HT Act covers England, Wales and Northern Ireland. There is separate legislation in Scotland – the Human Tissue (Scotland) Act 2006 – and the HTA performs certain tasks on behalf of the Scottish Executive (approval of living donation and licensing of establishments storing tissue for human application). The Human Tissue Act 2004 provides a framework for regulating the storage and use of human organs and tissue from the *living*, and the removal, storage and use of tissue and organs from the *deceased*, for many purposes including research. It establishes the Human Tissue Authority (HTA) and requires that a licence be obtained from the HTA to store 'relevant material' for scheduled purposes. 'Relevant material' means material take from a human body consisting of or including cells. A licence is needed to store relevant material for research except where held for a specific project with ethical approval from a REC.

The HTA issues codes of practice, which those undertaking activities related to human tissue must have regard to. These include a Code of Practice on Consent.

The Human Tissue (Scotland) Act 2006 deals *only* with the removal, storage and use of tissue and organs from the *deceased*. There is no equivalent body to the HTA and no licensing scheme.

The Acts make it a legal condition that research using human tissue has been approved by a REC in the following circumstances:

35.1.1 England/Wales/Northern Ireland

Storage or use of tissue for specific project on unlicensed premises.
Use of anonymised tissue from the living for research without specific consent for

research (e.g. surplus tissue taken in course of routine clinical care and anonymised to researcher).

Use of anonymised tissue for DNA analysis without specific consent.

35.1.2 Scotland

Use of organs retained from post-mortem examination carried out on the instructions of the Procurator Fiscal

The majority of public and patients are prepared to give samples for research.

35.2 Guidance

Human Tissue Authority (relevant in England / Wales) (accessed 10/2008) http://www.hta.gov.uk/guidance/codes_of_practice.cfm

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.'

35.3 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.

35.3.1 Results - Use of tissue in:

	Yes	No
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 'anonymised.' 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.

36.0 Annex 28: Informing Participants of Results: what should participants be told?

36.1 Summary

It would seem reasonable to argue that informing participants of results acknowledges their contribution, shows respect and sees them not simply as a means to the researchers' ends and there is a growing chorus of proponents of an ethical imperative to disclose results but there is no consensus yet.

Research indicates that most but not all subjects wish to hear the results of research, particularly those that might have personal consequence.

Researchers need to think separately about individual and general feedback and caution is needed in some cases.

36.2 Evidence

36.2.1 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.

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:

1. Feedback of results of randomised controlled trials can be part of an open and inclusive approach to participation in medical research.
2. The procedure for offering feedback should be considered at the start of a trial.
3. Results should only be sent to people who respond positively to such an offer and particular attention paid to feedback to potentially vulnerable groups.
4. The effect of feedback of sensitive information needs evaluation in a variety of contexts.
5. 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.

36.2.2 Some do not

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 discus the feedback of results. 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

36.2.3 The difficulty of interpretation

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.

36.2.4 Disagreement and a call for "case by case"

MacNeil, S.D., Fernandez, C.V., Offering results to research participants *British Medical Journal* **332** 189-190

An editorial written in response to Dixon Woods article by a team who clearly believe that provision of results is an ethical imperative. The author wrote an article entitled:

Fernandez, C.V., Kodisch, E., Weijer, C., (2003) Informing study participants of research results: an ethical imperative *IRB Ethics Human Research* **25** 12

Miller, F.A., et al (2008) Duty to disclose what? *Journal of Medical Ethics* **34** 210

The authors argue: “there is a fundamental lack of clarity about what to disclose that undermines any generalized ethical obligation.”

37.0 Annex 29: Capacity or Competence: how should they be assessed?

37.1 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 who take consent are able to identify whether a subject is competent to give such 'fair' consent. Presenting evidence of "capacity to assess capacity" through experience or training would help an application before an REC.

A person is unable to make a decision for himself if he is unable:

1. To understand the information relevant to the decision.
2. To retain that information.
3. To use or weigh that information as part of the process of making the decision, or:
4. To communicate his decision.

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 principal 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.

37.2 Guidance

Code of practice under the Mental Capacity Act (England and Wales) Chapter 4
http://www.opsi.gov.uk/acts/acts2005/related/ukpgacop_20050009_en.pdf

Royal College of Psychiatrists (UK)

The capacity to give consent is task- and time-specific, it constitutes a graded dimension of understanding, and it is something that can be influenced to some degree. Researchers should seek to help respondents achieve the capacity needed for the specific decision needed. Although, legally, a categorical decision on whether a person is competent to give consent is required, individuals whose capacity falls below that level should be helped to understand what is involved and to participate in decision-making. Ethics committees should satisfy themselves that the materials and process used to facilitate understanding are adequate.

USA Health and Human Services 1999 *Research Involving Individuals with Questionable Capacity to Consent*:
http://grants.nih.gov/grants/policy/questionablecapacity.htm

37.2.1 Points to Consider

Assessing Capacity to Consent.

Individual's capacities, impairments, and needs must be taken into account, in order to develop practical and ethical approaches to enable them to participate in research. Since well-validated and practical methods to assess capacity to consent are clearly needed, the NIH is supporting and will continue to support research addressing these issues. A clear understanding of the implications of various cognitive impairments, along with a careful consideration of proposed clinical research methodology, is required. Assessment is complex; simply answering a certain number of factual questions about a protocol may not be an adequate assessment. A key factor in participants' decision making is their appreciation of how the risks, benefits, and alternatives to participation in the study apply to them personally.

Limited decision making capacity covers a broad spectrum. A healthy person in shock may be temporarily decisionally impaired. Another may have been severely mentally retarded since birth, while yet a third who has schizophrenia may have fluctuating capacity. Researchers should be sensitive to the differing

levels of capacity and use assessment methods tailored to the specific situation. Further, researchers should carefully consider the timing of assessment to avoid periods of heightened vulnerability when individuals may not be able to provide valid informed consent.

Both IRBs and clinical investigators must keep in mind that decision-making capacity may fluctuate, requiring ongoing assessment during the course of the research. The consent process should be ongoing.

National Bioethics Advisory Committee Assessing Potential Subjects' Capacity to Decide about Participating in a Research Protocol

Recommendation 8. For research protocols that present greater than minimal risk, an IRB should require that an independent, qualified professional assess the potential subject's capacity to consent. The protocol should describe who will conduct the assessment and the nature of the assessment. An IRB should permit investigators to use less formal procedures to assess potential subjects' capacity if there are good reasons for doing so.

Medical Research Council (1991)

> *8.1 Many people with mental impairment or disorder are able to consent to their inclusion in research provided care is taken to explain it to them. When there is doubt about an individual's mental capacity, we recommend that a judgment on his ability to consent should be sought from the physician responsible. When the individual is not under the care of a physician, or the physician is involved in the proposed research, a view should be sought from a relative, friend or other person acceptable to the LREC.*

The legal position (recognising this will depend on the country and applicable law).

The High Court (England) held that an adult has capacity to consent if:

1. He or she can understand and retain the information relevant to the decision in question;

2. believe that information;
3. weigh that information in the balance to arrive at a 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 in two stages. Firstly does the person have an impairment of, or disturbance to, the mind or brain? Does this render the person unable:

1. To understand information relevant to the decision.
2. To retain that information.
3. To use or weigh that information.
4. To communicate a decision.

This is deemed to be situation specific.

Under the Act:

1. All are **assumed** to have capacity.
2. Before deciding someone does not have capacity, all steps must be made to enhance decision making.
3. A rash decision does not define incapacity.
4. 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.

National Research Ethics Service 2008. *Guidance on Participant Information Sheets*

Information sheets for adults without capacity

Both the Mental Capacity Act and the Medicines for Human Use (Clinical Trials) Regulations enshrine the ethical principle that any subject should be helped as

far as possible to be involved in the decision to participate, even where they do not have the capacity to give consent for themselves.

Potential subjects who have some capacity of understanding should therefore be provided with information about the research, its risks and benefits. The format and content of the information should reflect their capacity of understanding.

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.

37.3 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.

The MacCAT-T: a clinical tool to assess patients' capacities to make treatment decisions *Psychiatric Services* **48** 1415

An American tool to assess capacity.