DRAFT GUIDANCE – for consultation

DRAFT GUIDANCE

ON CONSENT BY A LEGAL REPRESENTATIVE
ON BEHALF OF A PERSON NOT ABLE TO CONSENT
UNDER THE MEDICINES FOR HUMAN USE
(CLINICAL TRIALS) REGULATIONS 2003

Purpose of this document

1. The European Union Directive on Good Clinical Practice in Clinical Trials 2001/20/EC (“the Directive”) concerns the conduct of clinical trials on medicinal products for human use. As part of its provisions, it requires consent to be obtained from the “legal representative” of a person who is unable to consent for him or herself prior to the participation of that individual in a clinical trial. Even in the emergency situation, it is still a requirement for such consent to be obtained.

2. However, the Directive does permit flexibility in implementing the provision, so that if necessary different arrangements can apply in different circumstances. Such flexibility is particularly important in the emergency situation. There is no intention that the implementation of the Directive should prevent ethical and necessary research in the emergency situation from continuing; such research is necessary to develop improved treatment and care for those in such situations.

3. The requirement of consent from a legal representative is a “procedural hurdle” which is in addition to the existing law governing medical interventions on persons not able to consent. The Medicines for Human Use (Clinical Trials) Regulations 2003 (“the Regulations”) will implement the Directive in the United Kingdom. After those Regulations come in to force, it will be necessary to satisfy the existing law governing consent to a medical intervention and have consent from a legal representative for a person to lawfully participate in a clinical trial within the scope of the Regulations. Further guidance on the existing law on consent can be found in the Department of Health’s Reference Guide to consent for examination or treatment (2001) which is available at www.doh.gov.uk/consent.
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4. This draft guidance aims to provide guidance on how the requirements for consent from a legal representative, as set out in Schedule 1 of the Regulations, will work in practice in England, Wales and Northern Ireland. In Scotland, the provisions of the Adults with Incapacity (Scotland) Act 2000 must also be considered.

5. Comments on the regulations themselves are being sought separately. Comments on this guidance – and on any additional material that it might be helpful to include - are sought by 16 May 2003.

Comments should be sent to: Dr Naomi Brecker
Clinical Ethics Branch
Department of Health
Room 536B Skipton House
80 London Road, London SE1 6LH
Email: Naomi.Brecker@doh.gsi.gov.uk
Introduction

1. The requirement of consent from a legal representative when a person is not able to consent for him or herself may be seen as having two main underlying purposes. The first reflects an increasing emphasis within society on the involvement of those close to a person in decision making about medical interventions. The second is to ensure that a decision concerning the participation of an individual in a clinical trial should be made as far as possible on an independent basis.

2. The draft Medicines for Human Use (Clinical Trials) Regulations 2003 ("the Regulations") aim to reflect these objectives. Wherever possible, it is envisaged that a person close to the patient will take on the role of a legal representative. However, in certain circumstances this may not be possible:
   - there may be no-one who is sufficiently close to the patient who is able and willing to take on this role; or
   - in emergency situations, it may be impossible to identify and contact a person close to the individual concerned before it is medically necessary to give the intervention.

3. Where it is not possible for a person close to the patient to be involved, the regulations envisage that the role of the legal representative will be fulfilled by the doctor responsible for the care of the patient, unless that person is “connected with the conduct of the trial” as defined in the Regulations (see paragraph 27 below). If the doctor is “connected with the conduct of the trial”, the health care provider which is responsible for the care of the patient must nominate someone who can act as a legal representative of the person concerned.

4. This guidance aims to assist those concerned with the implementation of the Regulations in developing good practice in implementing the provisions concerning the use of a legal representative. Because of the different practical considerations that arise, emergency and non-emergency situations are considered separately. Action to be taken if a subject subsequently recovers competence is covered in paragraphs 74-77.

5. The legal representative of the person is expected to base their decision on the subject’s “presumed will”. If the person has expressed their views on the specific clinical trial prior to the onset of incapacity, then there is no decision for the legal representative to make. Where a person suffers from a condition that is likely to lead to the development of incapacity, s/he may have considered the type of treatment – including clinical trials – that s/he would wish to receive at later stages of his or her illness. Schedule 1, Part 1 3(2)(b) makes clear that an “informed consent” given by the potential subject prior to the onset of incapacity will be legally valid, and hence the consent of a legal representative will not be required in addition. Likewise, if the potential subject has refused to enter the clinical trial prior to the onset of incapacity, that refusal must be respected.
6. It will be relatively unusual for a person to have received relevant information about a specific trial and made an advance consent or refusal in relation to that trial prior to the onset of incapacity. However, they may have made a more general advance refusal that would be applicable to a proposed clinical trial. As set out in paragraph 23, the legal representative should ensure that the advance refusal is respected.

Nomenclature

7. Where the participation in a clinical trial of a person not able to consent is considered, for the purpose of this document the person not able to consent is referred to as the “potential subject”. Once consent has been given by the mechanisms described below and the trial has commenced the person is referred to as the “subject”, the term which is used in the Regulations.

8. Although in the UK it is usual to refer to those who take part in clinical trials as “participants”, Directive 2001/20/EC on clinical trials refers to those individuals as “subjects”. The same term has been used in the Regulations and this Guidance for the purposes of compatibility with the Directive.

9. In this document, where a person close to the subject acts as a legal representative, that person will be described as a “personal legal representative” or PeLR. Where the role is filled either by the responsible medical practitioner or a person nominated by the health care provider that person will be described as a “professional legal representative” or PrLR. However, there is no requirement for a professional legal representative to belong to a specific profession; a lay person, such as a chaplain, may be able to act in this role.

NON-EMERGENCY SITUATIONS

10. Where a trial is to be conducted in a non-emergency situation on a research subject not able to consent, consent must be obtained prior to the subject’s participation in the trial:

- If the subject is a child, from a person with parental responsibility (ie person with PR is the personal legal representative (PeLR));
- If the subject is an adult, from the personal legal representative of that subject or, where there is no person available or willing to act as a personal legal representative, from the professional legal representative of the subject.
Personal legal representative

11. The Regulations specify that a person may be able to act as a legal representative for a subject “by virtue of their relationship” with the subject concerned, if they are available and willing to do so. (Schedule 1 (2)(a)(i)).

12. This means that a number of people may be capable of acting as a PeLR for a particular subject. For a child, the PeLR should be a person with parental responsibility. For an adult, it is suggested that the personal legal representative of an adult should be the person with the closest personal relationship with the potential subject who is capable him or herself of giving consent.

13. Persons who are not themselves capable of giving consent clearly are not able to give consent on behalf of another person. If, for example, a child incapable of giving consent is the person with the closest personal relationship to the potential subject then the person who is next closest would be an appropriate PeLR.

14. In most cases, the decision as to the person with the closest personal relationship with the potential subject will be straightforward. For example, the person may have a spouse or a long-standing partner with whom s/he or he is living. Confusion sometimes arises about the role of the “next of kin”. However, existing legislation that affords rights to the next of kin does not provide any uniform definition of that person. In this context, where the interests and welfare of the person him or herself are the central consideration, it is appropriate to give that role to the individual who may be most familiar with the personal wishes and concerns of the potential research participant. The Directive requires that consent be given on the basis of the subject’s “presumed will” (Articles 4a and 5a) and therefore an understanding of the subject’s probable views is necessary for the highest quality of decision-making.

15. In other situations the position may be less clear. The person may live on their own, and a number of family members or others claiming a personal relationship may come forward claiming that they should act as the PeLR.

16. The Regulations do not specify how the decision that a person should act as the PeLR is to be reached. In practice, it is suggested that the clinician in charge of the patient/potential subject’s care shall determine who should be regarded as the potential subject’s personal legal representative, unless that clinician is also an investigator or has another role in the research that may give rise to a conflict of interest. In such cases the determination shall be made by a professional of appropriate seniority involved in the potential subject’s care.
17. Given the importance of establishing who should act as the patient’s legal representative, the impartiality of the clinician is vital. It is hence important to avoid both conflict of interest and the perception of such conflicts. The Medical Research Council has issued guidance on conflict of interest in research.1 In reaching a decision, the clinician shall consult relevant members of the clinical team and those who appear to him/her to be closely interested in the potential subject’s welfare.

18. As a matter of good practice, most usually - if there were a dispute as to who should act as a PeLR - clinicians would not wish the potential subject to participate in the research; but sometimes this could be against the best interests of the potential subject concerned. In those circumstances, particularly if current treatment for the patient’s condition is of limited effectiveness, the clinician should consider approaching the Courts to make a determination of the most appropriate person to act as a PeLR.

19. In some circumstances, the person closest to the patient may not feel able to take on the role of PeLR. An example might be where the spouse of the person concerned would normally be the personal legal representative, but would prefer (perhaps because of distress caused by the spouse’s condition) that decisions were taken by another person, such as an adult child of the couple. Alternatively, the person might prefer the decision to be taken by professionals. The drafting of the Regulations means that either choice can be acted upon. Hence, there is a balance between ensuring that those close to the patient have the right to make decisions if they wish to do so, and ensuring the patient has the opportunity to benefit from a clinical trial if those closest to the person concerned do not wish to take a decision on participation.

20. The requirement that a person close to the patient should be “available” should not be taken to mean that the person must be physically present. In modern times, families may be more dispersed and it may not be feasible for the person closest to the patient to attend the health care facility where the potential subject is being treated. It is acceptable for the person to be contacted by telephone or other means of communication. If consent is obtained by telephone, it is good practice for the conversation to be witnessed and for both the person seeking consent and the witness to document the outcome in the relevant records. It is good practice to obtain a written record of the consent as soon as possible (for example, a consent form could be sent to the PeLR and returned by post).

21. In Scotland, the personal legal representative for an adult unable to consent for themselves is the adult’s guardian, welfare attorney or nearest relative as defined in the Adults with Incapacity (Scotland) Act 2000.

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1 Good Research Practice. Medical Research Council (2000), section 2.2.
Seeking consent from a personal legal representative

22. Once a personal legal representative has been identified, their consent to the subject’s participation in the clinical trial should be sought. They should be given an opportunity to understand the objectives, risks and inconveniences of the trial and the conditions under which it is to be conducted. They should be informed that their decision should be based on what the potential subject would have wanted him or herself, and that they have the right to withdraw consent to a subject’s participation at any time. A person who has agreed to act as a PeLR may find it helpful to have independent advice about their role, and it is good practice to ensure that this can be provided. Suitable independent sources of advice might be those who have undertaken the general preparation to act as a professional legal representative (see paragraph 33 below).

23. The personal legal representative should take into account any objections to the potential subject’s participation in research expressed by others close to the patient. The potential subject’s interest and welfare must always be the first consideration. Objections to participation in research may have various motivations; concern for the subject’s welfare would be one example, but the objector may have more personal reasons – for example, personal beliefs about research or medical treatment more widely. It may therefore not be appropriate for the objection of another person to over-rule participation in research that the PeLR believes the potential subject would have wanted to take part in.

24. Deciding what the person would have wanted is in many ways similar to the decision that a clinician needs to reach on the best interests of an incapacitated adult. The best interests of a person should not be equated with the best medical interests of the person. In the same way that a clinician reaching a “best interests” judgement in respect of the treatment of an adult unable to consent in England, Wales and Northern Ireland considers a range of factors, it may also be helpful for a PeLR to do so. These factors include:

- the person’s values and preferences when competent
- their physical and psychological health and well-being
- their quality of life
- their relationship with family and other carers
- their spiritual and religious welfare.

25. Where a person has made a valid and applicable advance refusal of treatment that covers the proposed clinical trial, this is regarded in law as evidence of the subject’s presumed will and it would be unlawful for a practitioner to treat a patient contrary to such a refusal. The PeLR should ensure that the terms of the advance refusal are respected.
Professional legal representative – the responsible clinician

26. Where there is no person who has a sufficiently close personal relationship with the potential subject is available and willing to act as a personal legal representative, the doctor responsible for the care of the patient will be the potential subject's legal representative unless the doctor is connected with the conduct of the trial.

27. The regulations define a person connected with the conduct of the trial as:
   a) The sponsor of the trial
   b) A person employed or engaged by, or acting under arrangements made with, the sponsor and who undertakes activities in connection with the management of the trial,
   c) An investigator for the trial (defined as the authorised health professional responsible for the conduct of the trial at a trial site, and if the trial is conducted by a team of authorised health professionals at a trial site, the leader responsible for that team),
   d) A health care professional who is a member of the investigator’s team for the purposes of the trial, or
   e) A person who provides health care under the direction or control of a person referred to in paragraphs c or d, whether in the course of the trial or otherwise.

28. The role of PrLR is separate from the doctor’s role in determining the appropriate health care for the patient, but both are founded on a concern for the patient’s welfare. Both the requirement of consent from a legal representative and the existing law on consent to medical interventions (which is not changed by the regulations) must be satisfied if the potential subject’s participation in the trial is to be lawful.

29. Prior to reaching a decision in the capacity of a legal representative, the doctor must receive relevant information about the trial (see paragraph 22 above). As previously noted, the Directive requires the decision of a legal representative to be based on the subject’s “presumed will”. Those with an interest in the patient’s condition, whether members of the care team or others with an interest in the patient’s welfare, may assist in determining what the person would want.

30. It is possible that the doctor could give consent, in his or her role as a legal representative, but know that participation would be unlawful because, for example, the subject’s clinical condition was such that participation in the trial would be very much against the person’s interests. Both decisions should be carefully documented. An example may be where the doctor has known a person with a terminal illness for some time, and become aware that their personality is such that they would take any chance for improvement, however small the chance. However, if the burdens and risks of the proposed trial are very high, and the person’s condition far advanced, it may clearly be against the person’s interests to participate.
Professional legal representative – the person nominated by the relevant health care provider

31. Where the doctor responsible for the potential subject’s care is connected with the conduct of the trial, as defined in paragraph 27 above, the relevant health care provider should ensure that a person is nominated who can take on the role of legal representative for a potential subject. To ensure the availability of an appropriate person, more than one person could be nominated by the health care provider as persons who may act as a legal representative.

32. The health care provider should ensure that a person who acts as a PrLR will have no actual or perceived conflict of interest when acting in that role. This means that the PrLR should be seen as independent of the research project. They should not be connected with the conduct of the trial as defined above, and should have no other role in the delivery and analysis of the research project, or the publication and further use of its results. The fact that the contribution of persons who act as a PrLR’s may be acknowledged in a publication does not in itself constitute involvement in publication. However, independence from the trial does not necessarily guarantee the absence of a conflict of interest (see paragraph 61). A range of individuals could potentially fulfil the role of a PrLR such as a chaplain, social worker, or member of PALS.

33. It is important that those who may act as PrLRs receive appropriate training. Such training will have both general and specific aspects. The general training should cover the role and responsibilities of a PrLR, and the general principles of clinical research. For example, the person should understand the concept of equipoise at the start of a clinical trial.

34. Prior to reaching a decision on whether to give or withhold consent to the entry of a potential subject in to a particular trial, the PrLR must be informed of the nature, objectives, significance, risks, inconveniences and implications of the trial, and the conditions under which it will be conducted (pursuant to article 3.2 (b) and (d) of the Directive), and the right to withdraw consent to a subject’s participation at any time.

35. For a particular trial, specific individuals will be identified who may be required to act as PrLRs in that trial. It will be acceptable for those individuals to receive information concerning the trial, and to have an interview with the investigator or a member of the investigating team at any time prior to considering the participation of an individual potential subject. If an individual subsequently acts as a PrLR for more than one potential subject in a trial, it shall not be necessary to repeat the interview or giving of information prior to considering the participation of each potential subject unless repetition is requested by the PrLR.
36. The PrLR shall, in reaching a view on the potential subject’s participation, consult any person that s/he views as appropriate who may contribute to the decision-making. As above, the decision must be made on the basis of the potential subject’s presumed will. As in paragraph 24 above, it may be helpful for the person to consider various aspects of the potential subject’s situation in reaching their decision. Although the PrLR should aim to gather sufficient information to enable them to make a reasonable judgement on the subject’s presumed will, there is no requirement to make exhaustive enquiries. There are similarities in this process to that undertaken by a clinician in reaching a view on an incapacitated adult’s “best interests”, which also requires (amongst other things) assessment of the person’s values and preferences, although these specific elements are central to the decision of a legal representative. The decision must be documented.

37. Consulting others will be particularly important when the person closest to the patient has chosen not to act as a PeLR and requested that the decision is taken by a PrLR. In other circumstances, where a number of people clearly have some personal knowledge of the patient, their knowledge about the patient’s attitudes may assist in decision-making. However, the right of the patient to confidentiality should not be forgotten; information may be sought from others without providing inappropriate details of the patient’s condition, treatment or potential treatment.

38. Where a person has made a valid and applicable advance refusal of treatment which covers the potential clinical trial, this should be regarded as conclusive evidence of the potential subject’s presumed will and the PrLR should ensure that its terms are respected.

Monitoring continued participation

39. The legal representative has the right to withdraw the subject from the trial at any time. This therefore implies a duty to check that a subject’s participation remains appropriate. Where the legal representative is either a person with a close relationship to the subject, or the responsible medical practitioner, the on-going contact with the subject will provide an opportunity for regular review. Significant changes in the subject’s condition, whether as a result of the trial or a change in the subject’s underlying medical condition, should as a matter of good practice lead to consideration of the continued appropriateness of trial participation.

40. Where the legal representative has been nominated by the health care provider, that person may not have regular contact with the subject outside the context of the trial which would afford opportunity for informal review. Therefore, specific arrangements should be made to ensure that the legal representative reviews the continued participation of the individual at appropriate intervals. The number of variables that may exist in the context of clinical trials is such that it is impossible to specify a single time limit for review that would be equally appropriate to all subjects. The variables may include the subject’s clinical condition, and whether the research involves a single administration of a treatment or a series of on-going interventions.
41. At the start of the trial, a maximum period for participation without further review by the legal representative shall be specified. The legal representative should ensure that s/he is clear about the review period for each subject to whom s/he is responsible. General guidance for the particular trial may be provided by the health service body that has nominated the legal representative, taking into account any views expressed by the research ethics committee following its consideration of the trial’s consent procedures.

42. Such general guidance should be refined by discussion with the medical practitioner responsible for the particular subject’s care in case the subject’s specific situation would indicate the need for an earlier review.

43. The doctor and clinical team responsible for the subject/patient’s care retain their normal duty of care to the patient. If they consider that on-going participation in the trial is no longer appropriate, for example because of a change in the subject’s condition or adverse effects, then they should advise the PrLR who will consider whether on-going participation is appropriate.

44. If the PrLR and the clinician disagree about the patient’s continued participation in the trial, the reasons for the disagreement should be clarified with the aim of finding a mutually acceptable solution in the subject’s interests. Such discussions should be documented.

45. Clinicians are not required to give clinically inappropriate treatment. If agreement cannot be reached, if the PrLR considers that on-going trial participation is appropriate but the clinician does not, the clinician should consider either handling over the care of the patient to a colleague or seeking legal advice. If appropriate, the Courts can be approached for a ruling regarding the patient’s treatment. Equally, if the PrLR wishes to withdraw the patient from the trial and the clinician considers that continued participation is in the patient’s best interests, legal advice should again be sought.

46. During the course of the trial, either the investigators or the clinical team may become aware of additional personal evidence concerning the patient’s previous wishes about research participation which would be relevant to the decision made by the legal representative (of whatever type). If the legal representative is not already aware of that evidence, it should be drawn to the legal representative’s attention. The legal representative should review the decision made in the light of the new evidence.

47. A professional legal representative becomes involved in giving consent on behalf of a potential subject when there is no person who is able to act as a PeLR by virtue of their relationship to that potential subject, and is available and willing to so act. In such cases, it is possible that during the course of a trial, a person who would be an appropriate PeLR may appear. If that person has an appropriate relationship with the adult, and is now available and willing to act as a PeLR, the person may take over the responsibility of acting as a legal representative of the subject. However, this in no way invalidates or alters the legality of interventions previously undertaken with the consent of the professional legal representative.
EMERGENCY SITUATIONS

Background

48. An accident, or the sudden onset of a condition (such as cardiac arrest) may result in incapacity. Such conditions may have high rates of mortality, and therefore research is required to improve treatment for those conditions. However, treatment may need to be initiated rapidly if it is to have any chance of being effective. In such circumstances it may not be feasible to contact someone who could act as a personal legal representative.

49. The CRASH trial is a good example of the type of research that may be required in the context of injury. This trial is an investigation of the use of corticosteroids within eight hours of a head injury that had impaired consciousness. Such injuries have a significant mortality and if the patient survives may give rise to significant neurological disability. Such evidence that exists suggests that the intervention needs to be given rapidly if there is to be any chance of benefit.

50. An example of research in to a condition of sudden onset is a recent pilot of thrombolytic therapy given to victims of cardiac arrest who have not been resuscitated with three defibrillating shocks. In theory, this may help to reverse the vascular “no reflow” phenomenon that may be hindering return of cardiac function. In this situation, expected mortality is very high. If the results of the full trial are as successful as the pilot, the intervention could potentially be a significant advance. In other situations, preliminary data may be available only from single arm pilot studies. It is important that research in these, and other situations where urgent resuscitation is required, are able to continue under the new arrangements.

51. In 1991, the U.S. Food and Drug Administration halted all research where prospective informed consent could not be obtained. Research in resuscitation, brain injury, and life threatening trauma came to a halt. The scientific community argued strongly that research in these areas was of paramount importance and that some mechanism must be developed to allow its continuance. In response to this void of clinical research, the FDA began a process in 1993 to allow emergency research to continue while still protecting the rights of the individual. The process culminated in November 1996 with the implementation of regulation 21 CFR 50.24 of the Federal Register. This regulation defines the conditions that must be met for Investigational Review Boards (IRB) to determine if a study qualifies for implementation without prospective consent and outlines a process for additional protection of the rights and welfare of subjects by mandating “community consultation” and “public disclosure”.

Department of Health March 2003
52. FDA regulation 21 CFR 50.24 states that:
   a) Research subjects must suffer from a life threatening disease process for which conventional or traditional therapy is minimally effective.
   b) Informed consent cannot be obtained from patients or next of kin because the therapeutic window of the drug or device being tested would preclude prospective consent. The researcher must document that that time spent trying to obtain consent extends from initiation of therapy to a point significantly beyond the therapeutic window. Investigators are still required to have a mechanism in place for obtaining prospective informed consent if the opportunity arose (i.e., a legally authorized representative is with the patient at the time of incapacitation).
   c) The research must have the potential to provide real and direct benefit to the patient, have a reasonable risk profile, and be supported by preliminary trials such as positive comparison or placebo-controlled.
   d) It must be documented that the research cannot be done practicably without the waiver.
   e) Under the direction of the IRB, the Investigator and IRB must enter into a dialogue with the community where the research is to take place. The investigator must disclose the details of the study, the criteria for enrollment, and the procedure for notification of participation. Comments from the community must be gathered and reviewed by the IRB.
   f) There must be disclosure to the patient and/or the next of kin that the patient participated in the study.
   g) There must be public disclosure of the study (i.e., media advertisements, town meetings, mailings, etc) before the initiation of the study as well as publicising the results after the study.

53. Although the procedure for community consultation appears reasonable, in practice it has proved difficult to implement, and apparently only limited feedback has been obtained from such approaches. Given the costs of conducting such consultation, it is not clear that the results achieved justify re-creating such an approach in the United Kingdom. This is not to dismiss the benefits of transparency; having information available on websites or in a form suitable for the public in the event of queries may help to ameliorate any suggestions of research on those unable to consent being carried out “in secret”.

The role of the legal representative in an emergency situation

54. The Directive allows no exception to the principle of consent from a legal representative prior to trial entry in any circumstances, and the United Kingdom is therefore required to give effect to this requirement. Nevertheless, it is our understanding that there was no intention that the Directive should stop ethical and necessary emergency research.
55. In an emergency, as with all medical treatment, the life and health of the potential subject is the first consideration. Unlike non-emergency situations, very little information may be available about the person – even the person’s identity may be unknown – to inform a judgement about the person’s presumed will.

56. If the potential subject is a child and it is feasible to seek consent from a person with parental responsibility then such consent must be obtained.

57. If the potential subject is an adult, and there is the possibility of a person close to the potential subject acting as a legal representative then this should be considered. However, the situation of that person needs to be considered carefully. If – for example – a couple have been involved in an accident in which the potential subject has been seriously injured, even if his or her partner has escaped serious injury the shock of the events may make it difficult for them to reach a balanced decision. Further, it should be recalled that the legal representative needs to have received information relevant to the subject’s participation (see paragraph 22 above) and it may not be feasible to provide this in the time before it is clinically necessary to deliver an intervention. Even if a person close to the patient is not able to act as a legal representative, they should be informed of the proposed interventions as far as possible.

58. The person close to the patient may provide information about the person’s values and preferences, or about the existence of an advance refusal of treatment, which should be taken in to account by any person acting as a professional legal representative. If it is clear that an advance refusal is valid and applicable to the circumstances this should be regarded as conclusive evidence of the potential subject’s presumed will.

59. It is most probable that in an emergency situation it will be necessary to seek the views of a professional legal representative. As in non-emergency situations, such a person can be either the doctor responsible for the health care provided to that adult (if not connected with the conduct of the clinical trial as defined in the Regulations, see paragraph 27 above) or a person nominated by the relevant health care provider.

60. In planning a trial, consideration will need to be given to who in practice could feasibly act as a legal representative. For example, in a trial of a new treatment for myocardial infarction that is designed to be delivered as quickly as possible after the event – for example in an ambulance – the paramedic in charge of the ambulance may be the only person who could feasibly act as a legal representative. Therefore, the health care provider will need to ensure that any paramedic who might be involved in the trial receives both the general and specific training concerning the trial as in paragraphs 33 and 34 above.
61. As noted in paragraph 32 above, the need to avoid conflict of interest should be taken into account in selecting persons who may act as a PrLR. However, the fact that a person is, and will not be, involved in the trial in any way should not lead to the automatic assumption that the person is independent, and has no “interest” in the trial. For example, professionals may sometimes disagree on whether equipoise truly exists in a particular trial; they may believe that the intervention to be offered in one “arm” of the trial is substantially better, or worse, than that to be offered in another arm. In such cases, it may be difficult for the person not to allow their personal beliefs about the trial to colour the decision that needs to be made on behalf of the patient. Such possibilities should be explored when considering the suitability of specific individuals for the role of a PrLR in a particular trial.

62. Different centres involved in a trial may choose to have different arrangements for ensuring that the role of legal representative is fulfilled; this is quite compatible with both the Directive and the Regulations. The health care provider may need guidance about the practicalities of delivering the trial intervention(s), and will need to ensure that those selected as potential PrLRs receive the relevant general and specific training.

63. In the absence of any information to the contrary, it is justifiable for a professional legal representative to assume that a potential subject would wish to receive an intervention which has the greatest chance of saving his or her life or improving (or minimising detriment to) his or her health. Where there is equipoise between standard treatment and a new treatment, and a clinical trial is being conducted, it may be reasonable to assume (other things being equal) that a potential subject would wish to enter a trial.

When the emergency is over

64. The limited basis on which the decision is made by a professional legal representative in an emergency means that review of the appropriateness of continued participation is particularly important. It may also be appropriate for another person to take over the role of legal representative.

65. If:
- the research involves continuing interventions, or will involve the obtaining of further personal data on the person concerned, and
- the subject is not expected to recover capacity to consent in the reasonably foreseeable future,
then as soon as possible after the subject’s entry into the trial the investigators shall determine whether there is a person capable of acting as the personal legal representative of the subject. As noted in paragraph 47, if a suitable PeLR comes forward spontaneously that person will take over the responsibilities of a legal representative.
66. If there is no person capable of acting as a PeLR, then it may be appropriate for the doctor responsible for the subject’s care to assume the role of the legal representative and the responsibility for reviewing the continued appropriateness of participation. However, it should be noted that consent from the original PrLR remains valid for the research project until it is countermanded by a refusal from a subsequent legal representative.

67. If there is no-one suitable to act as a PeLR but further information comes to the notice of the researchers or the clinical team (for example, concerning the patient’s likely views about participation in the research) the new information will need to be drawn to the attention of the current PrLR so that if appropriate the consent to participation that has been given can be reviewed.

68. As discussed in paragraphs 76-77 below, there will be the potential for bias to be introduced by either different degrees of effort made to locate a potential PeLR, or in the approach to seeking consent from a PeLR. The need to avoid this should be addressed as part of good governance of the trial.

69. Except in the situation described in paragraph 73 below, if a PeLR has been identified, consent from that person must be sought for:
   - any further intervention for the purposes of research alone,
   - any further collection of personal data or biological material for the purposes of research alone (ie if also necessary for clinical care, such data or materials can be collected),
   - the use of previously collected personal data or biological materials for the purposes of research alone.

70. If the PeLR refuses consent to the use of data/material already collected for research purposes alone, such materials must not be used for those purposes. If the data or materials are also necessary for the purposes of clinical care, their subsequent uses and disposal should accord with standard practice for clinical records and samples. As noted above, there is potential for bias to arise in the approach to a PeLR in these circumstances. The good practice guidance given in paragraphs 76-77 to enable refusal or withdrawal of consent to be audited would also be relevant in this situation.

71. If the data and materials are not necessary for the purposes of clinical care, the subject has died, and the PeLR refuses consent then the data and materials must be destroyed or respectfully disposed of.
72. If the data and materials are not necessary for the purposes of clinical care, and the subject remains alive, then the data and materials may be stored until trial closure.
   72.1 If the subject dies without recovering competence during this period, the materials and data must be destroyed or respectfully disposed of.
   72.2 If the subject recovers competence during that period, his or her consent must be sought to their use for research purposes according to the principles in paragraph 75.
   72.3 If the subject has not recovered competence by trial closure, the materials and data must be destroyed or respectfully disposed of.

73. Certain research studies involve interventions that for the purposes of consent need to be regarded as a single intervention or “specific care regime” (SCR). Failure to complete the specific care regime eg a course of antibiotics, or series of procedures, may compromise the patient’s health.

   73.1 If an adult subject recovers competence, s/he retains the legal right to refuse treatment in the middle of the specific care regime, in the knowledge of the potential harm to his or her health;
   73.2 If the subject does not recover competence, the consent from the professional LR will remain valid for the entire specific care regime;
   73.3 If a PeLR is identified, consent from the PeLR is required for:
       • any intervention not falling within the specific care regime,
       • any further collection of data or biological material for the purposes of research alone (ie if also necessary for clinical care, such data or materials can be collected),
       • the use of data or biological materials already collected in the research project.
   73.4 If there is no suitable person who is available and willing to act as a PeLR, the consent from the PrLR remains valid for the research project.
   73.5 The application to the research ethics committee (REC) must, where relevant, make clear which interventions fall within the specific care regime (SCR) and why failure to complete the SCR could compromise the patient’s health. The REC’s consideration of the proposed consent procedures should include whether any intended use of the SCR approach is appropriate.
RECOVERY OF COMPETENCE

74. If consent has been given on a subject’s behalf by a legal representative, whether personal or professional, and the subject subsequently recovers competence, they have the legal right to decide whether or not to continue participation in the trial. This situation may arise most frequently in respect of trials undertaken in emergency situations, but may also be relevant to non-emergency situations. The guidance below applies to both situations.

75. If and when a subject on whose behalf either a PeLR or a PrLR has given consent to participate in a research project recovers competence:
   - S/he must be informed of his/her participation and receive all information relevant to that participation;
   - His/her consent must be obtained to any further intervention, use of biological materials or data in the research project;
   - His/her consent must be obtained to the use of any personal data or biological materials already obtained in the context of the research project; if the subject refuses consent those materials or data must be respectfully disposed of or destroyed.

76. A proportion of patients may either die or not recover competence, and hence will not be able to withdraw from the trial. Those who recover may have received either the control or a trial intervention. It would be possible to introduce bias in the results by seeking consent after recovery in a manner that makes it more or less likely that a subject will withdraw. It is important that those responsible for seeking consent are aware of this possibility and minimise the risk of this occurring. As part of the governance procedures for the trial, audit of the process of seeking consent from those who have recovered may be helpful.

77. As a matter of good research practice, a record of the patient trial number (which is anonymous), the treatment allocated and the fact that consent was withdrawn should be kept. This will enable researchers to spot potential problems if withdrawals are not approximately equal in each intervention arm, are very much higher than expected, or are unusually high or low for particular centres. If possible, the reason for the withdrawal should also be recorded.
Indemnity

75. Persons who act as professional legal representatives will need assurances that they will be appropriately indemnified when they fulfill this role in good faith. This is particularly important when a PrLR takes a decision in an emergency situation and information subsequently becomes available that might indicate the decision made was inappropriate.

76. Disputes may also arise about a clinician’s (or where appropriate, another member of the team’s) choice of a PeLR. The clinician will need to ensure, as with his or her other duties, that adequate indemnity arrangements for this duty are in place.