EXPLANATORY MEMORANDUM TO

THE MEDICINES FOR HUMAN USE (CLINICAL TRIALS) AND BLOOD SAFETY AND QUALITY (AMENDMENT) REGULATIONS 2008

2008 No. 941

1. This explanatory memorandum has been prepared by the Medicines and Healthcare products Regulatory Agency, on behalf of the Department of Health, and is laid before Parliament by Command of Her Majesty.

This memorandum contains information for the Joint Committee on Statutory Instruments.

2. Description

2.1 This instrument amends the Medicines for Human Use (Clinical Trials) Regulations 2004 (the Clinical Trials Regulations) in order to: enable children to take part in emergency care trials when there would be no time to seek initial consent before administering the medicine; allow the Gene Therapy Advisory Committee to notify UKECA that its advice is not required on routine gene therapy trials and for applications to be transferred to another recognised ethics committee (EC) for an opinion; and modify the procedures for operation of ECs to widen the available expertise, reduce administrative burden and rationalise the documents an applicant must submit for an opinion.

2.2 This instrument also amends the Blood Safety and Quality Regulations 2005 (the Blood Regulations), in order to rectify drafting errors in the Blood Safety and Quality (Amendment) Regulations 2006.

3. Matters of special interest to the Joint Committee on Statutory Instruments

3.1 The drafting error that is addressed in regulation 9 was the subject of a Report of the Joint Committee on Statutory Instruments concerning the Blood Safety and Quality (Amendment) Regulations 2006 in the 1st JCSI Report of 2006-07.

4. Legislative Background

4.1 The Clinical Trials Directive (Directive 2001/20/EC) regulates clinical trials of medicines, including medicines under development, across the European Community. The Clinical Trials Directive was implemented in the UK by the Clinical Trials Regulations on 1 May 2004. The Parliamentary Scrutiny Committees considered the Clinical Trials Directive before agreement was reached by the Council of Ministers in 2001.

Emergency care trials

4.2 Article 4 (a) of the Clinical Trials Directive contains the general requirement that a minor cannot be included in a clinical trial without the consent of his/her parent or legal representative. Article 4(a) was implemented in the UK by regulation 28 of, and Schedule 1 to, the Clinical Trials Regulations so as to preclude a minor being included in a trial without prior consent of a person with parental responsibility or a legal representative in the UK. The Clinical Trials Regulations include a specific provision for establishing who can act as the legal representative.

4.3 These Regulations amend Schedule 1 and in doing so derogate from the general rule at Article 4(a) of the Directive. The amendment will allow minors to be entered in to a trial prior to consent having been obtained from a person with parental responsibility or legal representative in

trials of emergency medicines where - and whilst - certain conditions are met. This amendment mimics that already made to Schedule 1 in respect of incapacitated adults (whom are subject to a corresponding provision on proxy consent at Article 5a of the Directive (see S.I. 2006/2984)). This derogation from Article 4(a) is justified on the same basis as the earlier derogation from Article 5a namely that:

- the title of the Directive shows that it relates "to the implementation of good clinical practice in the conduct of clinical trials" and its underlying purpose is clearly to ensure trials are conducted in accordance with "good clinical practice" (see Article 1(4)). This is a set of internationally recognised requirements to be reflected in principles and detailed guidelines to be adopted and published by the Commission (see Article 1(2) and (3)).

- it is Directive 2005/28/EC (the Good Clinical Practice Directive) which lays down those principles. At recital (8) it states that the International Conference on Harmonisation's 1996 "Guideline for Good Clinical Practice" should be taken into account.

- this guideline was adopted by the Committee for Proprietary Medicinal Products in 1997 as applicable in Europe, and specifically envisages (at paragraph 4.8.15) that there will be emergency situations in which neither the trials subject's consent nor that of a legal representative can be obtained. The guideline is clear that trials may take place in such circumstances so long as suitable safeguards are contained in the trial protocol to protect the subject, and are approved by the relevant ethics committee.

4.4 The approach is also consistent with Commission correspondence with the UK which sees emergency situations as being for Member State to make provisions for and strongly implies that they are outside the scope of the Clinical Trials Directive. The approach is also consistent with that taken by France, Germany, Italy, Spain and Sweden.

Ethical review of trials

4.5 Article 6 of the Directive requires that Member States shall take the necessary measures for establishing and operating ethics committees. It further provides that an ethics committee shall give its opinion before a trial commences on any issue requested. Article 9 precludes a clinical trial being started until the ethics committee has issued a favourable opinion.

4.6 Article 9 is implemented by regulation 12 of the Regulations. By way of elucidation, Regulation 2 defines "ethics committee" and this term includes GTAC and committees established under the Regulations.

4.7 Under regulation 14(5) an application for an ethics committee opinion must be made to GTAC if the trial involves medicinal products for gene therapy (with one small and not relevant exception). Under regulation 15(1), GTAC is obliged to given an opinion on all such applications. Currently there is no flexibility for GTAC to pass applications to another ethics committee for review.

4.8 These Regulations amend regulation 15 to allow GTAC to give notice to the United Kingdom Ethics Committee Authority (UKECA) that it will not given an opinion on a particular application (in practice, because their expertise is not required); the outcome of serving such a notice is that the obligation on GTAC to review the trial is lifted, whilst UKECA becomes obliged to transfer the application to another ethics committee who in turn become obliged to provide an opinion. It remains the case that ethical review must be carried out within 90 days of the valid application being received.

4.9 These Regulations also amend regulation 15 to allow an ethics committee to give a conditional opinion.

4.10 Regulation 9 of the Clinical Trial Regulations provides that Schedule 2 to the Regulations (additional provisions relating to ethics committees) shall apply in relation to ethics committees (as defined in regulation 2). These Regulations also amend some of those 'additional provisions'.

4.11 Paragraph 1 of Schedule 2 defines an "expert member". These Regulations amend that definition so that those people with qualifications and/or experience relating to the conduct of "clinical research" (a broader term than "clinical trial") qualify as expert members.

4.12 Paragraph 6 of Schedule 2 (committees, meetings and proceedings) provides that an ethics committee can only determine an opinion at a full meeting for example where at least 7 members (at least one lay and one expert) are present. These Regulations amend that to enable a Chairman or a sub-committee to determine the final opinion where a full meeting has reached a provisional view and has delegated the task of reaching a final determination to the Chair or sub-committee.

4.13 Paragraph 7 of Schedule 2 (deputies and co-opted members) provides that an ethics committee may appoint deputies for expert or lay members. These Regulations amend that so that appointment of deputies is by the appointing authority (as defined).

4.14 Paragraph 8 of Schedule 2 (deputies and co-opted members) provides, amongst other things, that a) a person is eligible to be co-opted only if he is or has been a member of an ethics committee; and b) a co-opted member shall hold office for the meeting for which he is co-opted only. These Regulations amend those provisions to a) broaden eligibility to those who have advised on any committee advising on the ethics of research involving human subjects; and b) have co-opted members hold office in accordance with ethics committee standard operating procedures.

4.15 Finally, regulation 14(6) requires that an application for an ethical opinion must be accompanied by the particulars and documents specified in Part 1 of Schedule 3 to the Regulations. Paragraph 1(3) of Schedule 3 lists the documents that need to be provided with an application for ethical review. These Regulations amend that list.

4.16 The Blood Regulations impose safety and quality requirements on human blood collection and storage. The requirements apply to blood transfusion services in England, Scotland, Wales and Northern Ireland. Many of the provisions of the Regulations also apply to hospital blood banks. The Regulations implemented Directives 2002/98/EC and 2004/33/EC. The Blood Safety and Quality (Amendment) Regulations 2006 amended the Blood Regulations to implement Directives 2005/61/EC and 2005/62/EC which contain technical requirements with regard to blood and blood components.

5. Extent

5.1 This instrument applies to all of the United Kingdom.

6. European Convention on Human Rights

6.1 As the instrument is subject to negative resolution procedure and does not amend primary legislation, no statement is required.

7. Policy background

Amendments to the Clinical Trials Regulations

7.1 A full public consultation took place in 2005 on proposals to provide an exemption from the general rule that incapacitated adults can only participate in trials after the consent of their legal representative (as defined) has been obtained. Following the consultation, the exemption was

implemented by way of the Medicines for Human Use (Clinical Trials) Amendment (No.2) Regulations 2006, which came into force on 12th December 2006. Some of the responses raised the question of whether the exception to the general rule could also apply to children in the same situations and with the same safeguards. Advice was sought from the Commission for Human Medicines and its Paediatric Medicines Expert Advisory Group and, following a further public consultation, the attached instrument introduces similar provisions for trials of emergency care in children.

Emergency care trials

7.2 There are a number of serious illnesses that require urgent medical treatment to improve the chances of survival of the child. In these circumstances it is often impractical to obtain informed consent before entering a child into the trial. For example, in epilepsy, many children fit continuously so that they cannot breathe for long periods and are in danger of asphyxiation. Immediate medical treatment is needed to avoid death or severe brain damage. The existing medicines for these conditions are only partly successful and there is a need to conduct trials of new candidates, which have usually already been tested in adults.

7.3 The amending regulations provide an exception to the general requirement that informed consent must be obtained from a child's parents or legal representative prior to his/her participation in a trial. The exception applies only to clinical trials taking place in emergency situations where there is no time for informed consent to be obtained from a parent or legal representative. Informed consent must still be obtained as soon as reasonably practicable after the initial emergency and this would be a requirement of continued participation in the trial; but its absence would not preclude initial entry into a trial. The use of the exception would be subject to a safeguard; it could only be used in circumstances that have been approved by a EC.

Ethical review of trials

7.4 There are routine gene therapy applications for which the Gene Therapy Advisory Committee considers the research has matured to a point where its specialist ethical review is no longer required. The amending regulations modify GTAC's function by giving it the flexibility to focus its expertise on those clinical trials that warrant specialist review. This is achieved by enabling the United Kingdom Ethics Committee Authority (UKECA), following notification by GTAC, to direct that an application should be reviewed by another recognised EC.

7.5 A number of practical issues and anomalies have arisen in the implementation of the Regulations with respect to the membership and operation of UK ECs. The amending regulations address these and provide greater flexibility to ethics committees and their appointing authorities.

Consultation

7.6 The Government conducted a full 12-week public consultation on the proposals. This was circulated to over 2000 stakeholders and 52 responses were received from a range of organisations, including Primary Care Trusts, NHS Trusts, ECs, Royal Colleges, professional bodies and other bodies in the research sector. Of the 52 responses, 17 made no comment. The vast majority of substantive responses supported the aims of the legislative amendments although a number of comments were made on the proposals, particularly on the need for clear and comprehensive guidance in respect of the new arrangements across all three areas.

7.7 As a result of the responses to the consultation we opted to omit an original proposal to remove the review of gene therapy clinical trials for infectious disease from GTAC's remit as the apparent ambiguity in the legal definition of "gene therapy" has now been resolved.

Guidance

7.8 The National Research Ethics Service will publish revised Standard Operating Procedures (SOPs) for Research Ethics Committees, taking account of the changes to ethics committee procedure. GTAC will publish SOPs on arrangements for transfer of routine gene therapy applications. Detailed guidance on recruitment of children and adults into emergency trials will be published for consultation.

Consolidation

7.9 There are no plans to consolidate at this time.

Amendments to the Blood Regulations

7.10 Regulation 4(1)(d) of the Blood Safety and Quality (Amendment) Regulations 2006 inserted a new regulation 7(1)(g) in the Blood Regulations and regulation 6(2)(c) substituted a new regulation 9(1)(f) in those Regulations. These provisions impose a requirement to retain a record of certain events which may affect the quality or safety of blood and blood components. In the case of a blood establishment, the requirement relates to serious adverse events and is for a period of at least 15 years; in the case of a hospital blood bank, the requirement relates to serious events and is for a period of not less than 30 years.

7.11 The differences in period and terminology were the result of a drafting oversight, following a change of policy at a late stage of the drafting process. The policy decision was made to require retention of the data for a period of at least 15 years, but this was not reflected for hospital blood banks, as it should have been, in the final draft. Regulation 8 replicates the wording of regulation 7(1)(g) in regulation 9(1)(f) of the Blood Regulations.

7.12 Since the amendment will bring consistency in the requirements to retain a record of serious adverse events which may affect the quality or safety of blood and blood components, reflecting the original policy intention at the time that the 2006 Regulations were made, as consulted upon at the time, it was not felt necessary to re-consult on this amendment.

7.13 The amendments made in regulation 7 and 9 address other, minor, defects in the Blood Regulations.

Consolidation

7.14 There are no plans to consolidate at this time.

8. Impact

8.1 An Impact Assessment on the amendments to the Clinical Trials Regulations is attached to this memorandum.

8.2 The impact on the public sector is nil.

9. Contact

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The Blood Regulations

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Summary: Intervention & Options

Department /Agency:	Title:	
Medicines and Healthcare products Regulatory Agency	**Impact Assessment of Amendments to the Medicines for Human Use (Clinical Trials) Regulations 2004**	
Stage: Final	**Version:** 3	**Date:** 26 **March 2008**
Related Publications: RIAs for Regulations implementing the Clinical Trials Directives and the subsequent amendments MLX 340		

Available to view or download at:

http://www.mhra.gov.uk

Contact for enquiries: Brian Davis **Telephone:** 01768 779 640

What is the problem under consideration? Why is government intervention necessary?

Unnecessary restrictions and administrative procedures could discourage research in the UK by the pharmaceutical industry to identify essential new medicines

What are the policy objectives and the intended effects?

The proposed amendments to the UK Clinical Trials Regulations (the Regulations) would (a) enable Minors who require emergency care to participate in clinical trials of new treatments that might improve their chances of survival, and benefit future minors by improving treatments that require emergency care (b) make available more resource to GTAC to provide ethical review of complex gene therapy trials; and (c) widen the expertise available to RECs and rationalise the documents an applicant must submit for an opinion

What policy options have been considered? Please justify any preferred option.

(a) Continue with the current arrangements. This would not achieve the policy objectives

(b) Interpret the current legislation in guidance. There is no flexibility to do so because detailed requirements are included in the Regulations

(c) Amend the current legislation (preferred). Therefore amending the Regulations is considered the preferred option.

When will the policy be reviewed to establish the actual costs and benefits and the achievement of the desired effects? 05/2011

Ministerial Sign-off For Final proposal/implementation stage Impact Assessments:

I have read the Impact Assessment and I am satisfied that, given the available evidence, it represents a reasonable view of the likely costs, benefits and impact of the leading options.

Signed by the responsible Minister:

Dawn Primarolo .....Date: ***31st March 2008***

Summary: Analysis & Evidence

Policy Option: 3	Description: Amending the Regulations

COSTS

ANNUAL COSTS	Description and scale of **key monetised costs** by 'main affected groups'
One-off (Transition) **Yrs**	
£ 0	
Average Annual Cost (excluding one-off)	
£ 0	**Total Cost** (PV) **£ 0**

Other **key non-monetised costs** by 'main affected groups'

BENEFITS

ANNUAL BENEFITS	Description and scale of **key monetised benefits** by 'main affected groups'
One-off **Yrs**	
£ 0	
Average Annual Benefit (excluding one-off)	
£ 0	**Total Benefit** (PV) **£ 0**

Other **key non-monetised benefits** by 'main affected groups'

Key Assumptions/Sensitivities/Risks It is assumed that making the regulatory system more efficient will benefit the pharmaceutical industry by more rapid development of new medicines which in turn will allow companies to market them sooner and improve their business returns

Price Base Year	Time Period Years	**Net Benefit Range** (NPV) **£ 0**	**NET BENEFIT** (NPV Best estimate) **£ 0**

What is the geographic coverage of the policy/option?				UK	
On what date will the policy be implemented?				May 2008	
Which organisation(s) will enforce the policy?				UKECA, MHRA	
What is the total annual cost of enforcement for these organisations?				£	
Does enforcement comply with Hampton principles?				Yes	
Will implementation go beyond minimum EU requirements?				No	
What is the value of the proposed offsetting measure per year?				£ 0	
What is the value of changes in greenhouse gas emissions?				£ 0	
Will the proposal have a significant impact on competition?				Yes/No	
Annual cost (£-£) per organisation (excluding one-off)	Micro **0**	Small **0**	Medium **0**	Large **0**	
Are any of these organisations exempt?	Yes/No	Yes/No	N/A	N/A	

Impact on Admin Burdens Baseline (2005 Prices) (Increase - Decrease)

Increase of £ 0 Decrease of £ 0 **Net Impact** **£** 0

Key: **Annual costs and benefits: Constant Prices** **(Net) Present Value**

Evidence Base (for summary sheets)

[Use this space (with a recommended maximum of 30 pages) to set out the evidence, analysis and detailed narrative from which you have generated your policy options or proposal. Ensure that the information is organised in such a way as to explain clearly the summary information on the preceding pages of this form.]

1. TITLE OF PROPOSAL

Amendment of the Clinical Trials Regulations as amended (the Regulations) to allow clinical trials of emergency care for children and modify the operation of, and procedures relating to, the Gene Therapy Advisory Committee (GTAC) and research ethics committees (RECs).

2. PURPOSE AND INTENDED EFFECT OF MEASURE

(i) The objective

To modify the Regulations to allow clinical trials of emergency care for children and improve the operation of, and procedures relating to, obtaining an opinion of a research ethics committee or GTAC.

The proposed amendments to the Regulations would (a) enable children to take part in emergency care trials when there would be no time to seek initial consent and fulfil the other requirements before administering the medicine (b) modify the role of GTAC to allow GTAC to notify UKECA that its advice is not required on routine gene therapy trials and for applications to be transferred to another recognised REC for an opinion; (c) modify the definition of expert member of an ethics committee to include those involved in clinical research in general; and (d) provide powers for the Chair and/or sub-committees of an ethics committee to issue the final opinion of the committee

(ii) Background

(a) Emergency research in children amendment

In December 2006 the Government amended the Regulations to enable incapacitated adults to take part in emergency care trials when there would be no time to seek initial consent before administering the medicine.

Nine respondents to the consultation proposed that the amendment should also apply to clinical trials in minors where urgent action was required. However, the Government needed to consult on that question specifically before the Regulations could be amended.

There are a number of serious illnesses that require urgent medical treatment to improve the chances of survival of the child. In these situations it is often impractical to obtain informed consent before entering a child into the trial. For example, in epilepsy, many children fit continuously so that they cannot breathe for long periods and are in danger of asphyxiation. Immediate medical treatment is needed to avoid death or severe brain damage. The existing medicines for these conditions are only partly successful and there is a need to conduct trials of new candidates, which have usually already been tested in adults

The proposed amendment would allow a minor to participate in an emergency care clinical trial prior to consent having been obtained from a person with parental responsibility or his/her legal representative provided that an ethics committee has approved the trial. Informed consent would still be a requirement of participation but its absence would not preclude initial entry in to a trial. The normal arrangements for seeking consent would need to be met as soon as reasonably practicable. The exception could not be used if there is no longer an emergency and immediate steps would have to be taken by the investigator or clinician responsible for the care of the patient to obtain valid consent to the continuing participation of the minor in the trial.

Before reaching a decision on the ethical acceptability of the trial the ethics committee would need to consider the proposed exception from the need for prior consent and the overall

arrangements for obtaining informed consent. The healthcare worker who is providing emergency treatment related to the clinical trial will need to be provided with a detailed protocol – such as inclusion and exclusion criteria - that fully reflects the recommendations of the Ethics Committee that has approved the trial protocol.

We sought advice from the independent expert advisory group on Paediatrics (PAEG) and from the Commission for Human Medicines (CHM), both of which advise the Secretary of State for Health on these matters. The PAEG and CHM both advised that the proposed amendment was appropriate but agreed that the proposed provisions should require an appropriate ethics committee to approve the protocol describing the proposed procedure for including participants. The provision includes such a requirement.

(b) Add flexibility to the role of GTAC

At present, the Regulations require all gene therapy clinical trials to be approved by the Gene Therapy Advisory Committee (GTAC). GTAC's expertise as a specialist committee lies in its ability to advise on the acceptability of novel approaches of gene therapy research. However, as the technology progresses constantly, clinical experience with some gene therapies is becoming more routine and some research has matured to a point where GTAC specialist ethical review is no longer required. It is proposed therefore to add flexibility to the role of GTAC by enabling the United Kingdom Ethics Committee Authority (UKECA), following notification by GTAC, to direct that routine gene therapy applications which do not require specialist review should be reviewed by another recognised REC.

(c) Amendments to UK research ethics committees'(REC) procedures

A number of practical issues and anomalies have arisen in the implementation of the Regulations. The proposed amendments would address these and provide greater flexibility to ethics committees and their appointing authorities.

Expert members

The definition of an expert member in the Regulations is limited to those involved in clinical research on medicines. It is proposed to modify this definition to include those involved in clinical research in general, because RECs consider many types of clinical research not involving medicines. This would widen the range of expertise and perspective on the committee but would not affect the balance of expert and lay members.

Final opinion of a research ethics committee

The Regulations currently do not provide clear powers for the Chair and/or sub-committees of a REC to issue the final opinion of the committee where a provisional opinion has been given in a full meeting and an applicant has responded to a request for further information. Providing these powers would avoid the unnecessary delay in waiting for the next full meeting.

Conditions when giving a favourable opinion

The regulations do not allow a REC to grant a favourable opinion subject to specific conditions being met. Providing such a power would enable opinions to be issued more promptly. There is already provision for the licensing authority to grant a clinical trial authorisation subject to conditions.

Operation of research ethics committees

The Regulations make the REC itself responsible for appointing deputy members. The proposed amendment would make the appointing authority responsible, ensuring the same standards of appointment for members and deputy members and the provision of indemnity for deputy members.

Currently the Regulations restrict those who can be co-opted as members to those who have previously been a member of an ethics committee as defined by the Regulations. The proposed

amendment would allow greater flexibility in co-opting members while requiring that procedures are set out in the committee's SOPs; and

The Regulations stipulate the documents that must be submitted with and application to a REC. The proposed amendment would rationalise the information applicants must send to the ethics committee by omitting documents reviewed only by the MHRA (e.g. relating to manufacture and import of the trial product).

(iii) Risk to public health

(a) Emergency care in children is an important part of public health. For example the immediate treatment of common health hazards, such as head injury, cardiac arrest and status epilepticus, can improve survival and subsequent health. Preventing research into new treatments for emergency care in children (the hazard) could lead to unnecessary deaths and morbidity from conditions requiring effective or urgent treatment (the harm). As with any medicine, the benefits to minors must be offset by the costs upon those who, in the event, experience adverse reactions to the new treatments. It is not possible to quantify the proportion of minors who will experience reactions as a result of the change; however it is the responsibility of the ethics committees to grant a favourable opinion only where these risks are acceptably small. Based on the parallel provision introduced in 2006 in relation to incapacitated adults, the numbers of minors affected by these provisions is likely to be negligible.

(b) Unnecessary expert assessment of the ethical aspects of gene therapy clinical trials by GTAC, which takes longer that an ordinary REC, can slow the approval of a clinical trial and thus delay its start (the hazard) which could lead to slower development of essential new medicines and deter sponsors from conducting research into essential new medicines (the harm).

(c)Unnecessary restrictions on the operation of RECs could make the assessment of applications for clinical trials more complex and prolonged than needed (the hazard) which may deter sponsors from conducting research into essential new medicines (the harm).

3. OPTIONS

(i) Option 1: Continue to rely on existing arrangements

(a) The Clinical Trials Regulations require that the informed consent of a minor's (children less than 16 years) legal representative is obtained prior to his/her inclusion in a clinical trial. Continuing to rely on these arrangements would prevent minors from participating in certain trials of emergency care and therefore from benefiting from research into new treatments.

(b) GTAC's expertise as a specialist committee lies in its ability to advise on the acceptability of novel approaches of gene therapy research. At present, the Regulations require all gene therapy clinical trials to be approved by the Gene Therapy Advisory Committee. Continuing this arrangement would require GTAC to review some gene therapy applications that no longer require their expert specialist ethical review.

(c)The operation of RECs: (1) The definition of an expert member in the Regulations is limited to those involved in clinical research on medicines. Continuing this requirement would restrict the range of expertise and perspective on the committee. (2) The Regulations currently do not provide clear powers for the Chair and/or sub-committees of an ethics committee to issue the final opinion of the committee where a provisional view has been given in a full meeting and an applicant has responded to a request for further information. Continuing this arrangement would result in unnecessary delay in waiting for the next full REC meeting. (3) The regulations do not allow an ethics committee to give a favourable opinion subject to conditions. Providing such a power, could prevent the committee delaying the issue of its opinion where it is satisfied the trial is ethical but wishes, for example, to see further evidence on certain points. (4) The regulations give the committee itself responsibility for appointing deputy members rather than the appointing authority. Continuing this arrangement would fail to ensure the same standards of appointment as for members and the provision of indemnity for deputy members. (5) Currently

the Regulations restrict those who can be co-opted as members to those who have previously been a member of an ethics committee as defined by the Regulations. Continuing the proposed arrangement would prevent a REC co-opting members with important expertise and experience. (6) The Regulations stipulate the documents that must be submitted with an application to a REC. Keeping the current requirement would result in applicants sending documents to the ethics committee for review that are aimed at experts in the MHRA (e.g. relating to manufacture and import of the trial product).

(ii) Option 2: Interpret the current legislation in guidance

There is no flexibility to interpret the legislation in guidance because specific detailed requirements are included in the Regulations as set out below.

(a) Consent on behalf of a minor

Article 4(a) of the Clinical Trials Directive provides for a general rule that minors may only be included in a clinical trial if the informed consent of the parents or legal representative has been obtained.

This requirement has been implemented in the Regulations. Regulation 28 requires that a trial must be conducted in accordance with the "conditions and principles of good clinical practice". By virtue of regulation 2(1), these conditions and principles are set out in Schedule 1. Part 4 of Schedule 1 applies to minors. Paragraph 4 of Part 4 requires that informed consent must be given by a person with parental responsibility or a legal representative before a minor can participate in a trial. Paragraphs 1-3 & 5 contain various other information requirements that must also be met before a minor can be entered in a trial. Currently there are no exceptions to these requirements; if a minor is entered into a trial without these requirements being met first, a criminal offence has been committed (reg 49(1)(d)).

(b) Amending the scope of GTAC review

The Gene Therapy Advisory Committee's (GTAC's) expertise as a specialist committee lies in its ability to advise on the acceptability of novel approaches of gene therapy research. At present, the Regulations require all applications for ethical approval of gene therapy clinical trials to be made to GTAC (regulation 14(5)). GTAC is then obliged to determine each of those applications (regulation 15).

(c) Expert Research Ethics Committee (REC) Members

The definitions of expert and lay members in Part 1, Schedule 2 of the Regulations restrict the expertise available to a research ethics committee. A person does not qualify as an expert member unless he is a health care professional, has professional qualifications or experience relating to clinical trials, or has been a registered doctor or dentist. At the same time, a person cannot be a lay member if he conducts clinical research.

The combined effect of these provisions is to exclude completely from possible membership of an ethics committee a person who is not a health care professional and has experience in conducting clinical research but not medicinal trials.

(d) Procedures for giving a research ethics committee (REC) opinion

Currently paragraph 6(4) of Schedule 2 requires a REC meeting with 7 members to determine an opinion. The effect of the requirement to give the "final opinion" at a further meeting with 7 members present increases the workload at committee meetings and delays the issue of the opinion.

(e) Favourable research ethics committee opinion subject to conditions

The Regulations stipulate the requirements for research ethics committees, meetings and procedures in Schedule 2 paragraph 6(4). There is no provision for the ethics committee to give a favourable opinion subject to conditions. This prevents the committee from issuing a favourable opinion more promptly in cases where it does not require further information or any

significant change to the application before determining its opinion, but only wishes to add remarks.

(f) Procedures for appointing deputy members

In the current Regulations, whereas Schedule 2 paragraph 3(3) requires the appointing authority to appoint full members, Schedule 2 paragraph 7(1) provides for an ethics committee to appoint persons to act as the deputy of an expert member or lay member. Thus there are different standards for appointing members and deputy members of a research ethics committee.

(g) Co-opting members to a research ethics committee

Schedule 2, paragraph 8(3) allows a person to be co-opted as a member only if he is or has been a member of an ethics committee as defined in the Regulations. From the definition of "ethics committee" in Regulation 2, this prevents the co-opting of members or former members of ethics committees that are not recognised under the Regulations.

(h) Extension of duration of office for co-opted members

Currently a co-opted member may only hold office in relation to the meeting for which he or she is co-opted by the committee as stipulated by Schedule 2, paragraph 8(5). The provision in paragraph 8(5) means that a separate letter must be issued in relation to each meeting attended by the co-opted member. This creates an unnecessary administrative burden.

(i) Reduction of documentation required in an application to an ethics committee

Schedule 3 Part 1 sets out the particulars and documents that must accompany an application for an ethics committee opinion. This is done by cross-reference to the documents that must be submitted with a CTA application which are listed in Part 2 of Schedule 3.

Experience has shown that the following items of information that the Regulation requires an applicant to submit to a research ethics committee for an opinion are unnecessary:

- Details of competent authorities to which requests for authorisation have been made in other Member States (Schedule 3 Part 2 paragraph 4).
- Details of the person responsible for manufacture or importation of any investigational medicinal product and details of any authorisation referred to in Article 13 of the Directive held by that person (Schedule 3 Part 2 paragraph 7).
- The address of the premises at which any IMP has been, or is to be, checked in accordance with Article 13(3) of the Directive, and in the case of importation from outside the EEA a statement from the qualified person giving details of the manufacture or assembly (Schedule 3 Part 2 paragraph 8).
- A description of the proposed clinical trial (Schedule 3 Part 2 paragraph 9)

The data in paragraphs 4, 7 & 8 of Part 2 of Schedule 3 are not listed in the Directive, the Commission guidance or ICH GCP as requirements of the application to the ethics committee.

(iii) Option 3: Amend the Clinical Trials Regulations.

(a) Consent on behalf of a minor: The proposed amendment would allow a minor to participate in an emergency care clinical trial prior to: (1) consent having been obtained from a person with parental responsibility or his/her other legal representative; and (2) various other information requirements have been fulfilled. The use of this exception to the normal consent requirements is to be safeguarded by a requirement that the trials – including the use of the exception – must have been approved by an ethics committee. Informed consent would still be a requirement of participation but its absence would not preclude initial entry in to a trial. The normal arrangements for seeking consent would need to be met as soon as reasonably practicable. The exception could not be used if there is no longer an emergency and immediate steps would have to be taken by the investigator or clinician responsible for the care of the minor to obtain valid consent to the continuing participation in the trial.

(b) Amending the scope of GTAC review: The proposed amendment would add flexibility to the role of GTAC by enabling the routine applications which do not require specialist review to another recognised REC. The provision for transfer of routine trials would allow the Committee to continue to focus on novel, challenging, gene therapy approaches thereby enabling it to continue its important function as ministerial advisory body for gene therapy research and to act as a source of expert advice to researchers and other RECs.

(c)Expert Member: It is proposed to modify the definition of an expert member to include those involved in clinical research in general, because RECs consider many types of clinical research not involving medicines. This would widen the range of expertise and perspective on the committee but would not affect the balance of expert and lay members.

(d) Final opinion of a REC: Amending the Regulations to provide clear powers for the Chair and/or sub-committees of a REC to issue the final opinion of the committee where an applicant has responded to a request for further information would avoid the unnecessary delay in waiting for the next full meeting of the REC.

(e) Conditions when giving a favourable opinion: Amending the regulations to allow a REC to give a favourable opinion subject to conditions would enable opinions to be issued more promptly where the committee is satisfied the trial is ethical but wishes, for example, to see further confirmatory evidence on certain points.

(f) Co-opted Members: Amending the Regulations to widen the expertise of those who can be co-opted as members while requiring that procedures are set out in the committee's SOPs would allow greater flexibility in co-opting members and provide additional expertise for RECs.

(g) Documents that must be submitted to a REC: Amending the Regulations that stipulate the documents that must be submitted with and application to a REC by omitting documents reviewed only by the MHRA (e.g. relating to manufacture and import of the trial product) would reduce the information applicants must submit to the ethics committee.

4. BENEFITS

(i) Option 1: Continue to rely on existing arrangements

Nil

(ii) Option 2: Interpret the current legislation in guidance

- Introducing new guidance instead of amending the Regulations would not achieve the objective because these matters are expressly provided for in the Regulations; guidance can only clarify, not alter, express legislative requirements.

(iii) Option 3: Amend the Regulations

(a) The proposed amendments to the Regulations would benefit:

- minors who require emergency care by allowing them to participate in clinical trials of new treatments that might improve their prospects of recovery and survival;
- future minors by improving treatments for conditions that require emergency care;
- UK researchers by allowing them to participate in multinational trials of emergency care treatments for children's conditions;
- Public health by providing the opportunity to reduce mortality and morbidity of children's conditions requiring urgent treatment;
- The UK pharmaceutical industry by allowing them to develop new essential medicines for emergency care of children as part of their business;
- Sponsors of gene therapy trials not involving novel approaches by simplifying their ethical review;
- Those conducting complex gene therapy trials by providing GTAC more resource to consider them.

- Sponsors of clinical trials seeking ethical review by providing additional expertise, reducing the information to be submitted and speeding the review procedures; and
- Deputy members of RECs by providing indemnity for them.

5. BUSINESS SECTORS AFFECTED

(a) The innovative pharmaceutical industry will be affected.

(b) There will be a limited impact on the generic sector.

(c)The NHS, universities, charities and others who undertake non-commercial clinical trials of emergency care will also be affected.

6. ISSUES OF EQUITY OR FAIRNESS

(a) The proposed Option 3 will provide minors with the same opportunities as incapacitated adults to benefit from advances in emergency treatments for conditions that could cause prolonged disability or death.

(b) Is it fair under Option 1:

- to exclude minors who need emergency care from clinical trials that might improve their chance of recovery or survival?
- to exclude future minors from advances in treatments for emergency care that derive from clinical trials?
- to prevent UK researchers from participating in multinational trials of emergency care treatments for minors?
- to prevent the UK pharmaceutical industry from developing new medicines for emergency care of minors as part of their business?
- to prevent GTAC from notifying UKECA that its advice is not required on routine gene therapy trials and for applications to be transferred to another recognised REC when GTAC's special expertise is no longer needed to provide an ethical opinion?
- to prevent a REC from widening its expertise by including expert members with experience of clinical research other than with medicines?
- to prevent a REC from reducing unnecessary delays to giving their opinion by allowing the Chair and/or subcommittees to issue the final opinion where a full meeting has given a provisional review and the applicant has responded to a request for further information?
- to prevent a REC from reducing unnecessary delays to giving their opinion subject to conditions when giving their opinion when this procedure is already available to the licensing authority?
- to have standards for appointing members that differ from those for appointing deputy members resulting in an unnecessary administrative burden to provide indemnity for deputy members?
- to require applicants for an ethics committee opinion to provide documents that are not required by the REC in forming its opinion?

7. COSTS

(i) Anticipated Costs under option 1: *Continue to rely on existing arrangements*

Nil

(ii) Anticipated costs under option 2*: Interpret the current legislation in guidance*

There is no flexibility to interpret the legislation in guidance because specific detailed requirements are included in the Regulations (see subparagraphs 3(ii)(a-i)) therefore anticipated costs are not discussed.

(iii) Anticipated costs under option 3: *Amend the Clinical Trials Regulations*

(a) Activities for which fees are proposed

The proposed amendments would not trigger any additional fees because fees are not charged for applications to ethics committees.

(b) Costs of commencing and conducting a clinical trial to conform with the amended Regulations

(1) Costs of implementing changes to the requirement to obtain consent prior to entering a minor into a trial of medicines for emergency care

This option would not change the current direct costs for pharmaceutical companies, medical research charities, universities or NHS Trusts. The proposed amendment would remove the requirement for (1) consent from the legal representative of a minor prior to entering him or her into a trial of medicine for emergency care and (2) fulfilling other information requirements that must be met before a minor can be entered in a trial. It would also require that consent is sought from a person with parental responsibility or the minor's legal representative as soon as reasonably practicable. As this is the current requirement before entering a minor into a trial it should not involve any additional costs. This type of research is currently permitted in several other EEA countries (see subparagraph 9(ii) (a) below for details).

(2) Costs of implementing changes to the requirements for applications to GTAC

The proposed amendment would also allow GTAC to delegate applications for routine gene therapy applications to another recognised REC. The National Research Ethics Service (NRES) would co-ordinate this procedure. There would be no additional administrative costs to the applicant.

(3) Costs of implementing the changes to the procedures for RECs

This option would leave the current direct costs for pharmaceutical companies, medical research charities, universities or NHS Trusts unchanged (items 1-5) or reduced (item 6). The proposed amendments would allow: (1) experts with wider experience to be appointed to RECs, (2) the Chair of a subcommittee to issue the RECs final opinion, (3) RECs to impose conditions on applicant or conduct of the trial when issuing their final opinion, (4) the appointing authority to appoint deputy-members instead of the REC, (5) a REC member to be co-opted who has previous relevant experience but was not previously a member of a recognised REC. and (6) a reduced package of documents as part of an application for an ethics committee opinion. The proposed amendments (1-5, above) would not involve increased direct costs but may reduce costs indirectly by making the procedure of issuing a final opinion of a REC more rapid and allowing more efficient development of new medicines The proposed amendment (6) could reduce direct costs by reducing the number of documents that need to be included in an application to a REC.

8. CONSULTATION WITH SMALL BUSINESS: THE SMALL FIRMS' IMPACT TEST

Since we do not anticipate any added burden resulting from the proposed amendments we have not consulted small businesses separately. We included small businesses in the groups to whom we distributed the consultation letter and partial Regulatory Impact Assessment. We specifically asked them to comment on any issues of increased costs or other impacts in their responses but we did not receive any comments on costs.

9. COMPETITION ASSESSMENT

(i) Market affected

(a) The proposed amendments to the Regulations will affect:

- The innovative pharmaceutical industry.
- There will be a limited impact on the generic sector.
- The NHS, universities, charities and others who undertake non-commercial clinical trials will also be affected

(ii) The clinical trials market

(a) Organisations such as research-based pharmaceutical companies, commercial trial centres acting under contract, and a range of non-commercial bodies such as universities, the NHS, and medical research charities undertake most clinical trials. Trials undertaken by or on behalf of pharmaceutical companies comprise the majority of trials and are conducted on a commercial basis. The impact of the amendment is likely to affect competition because the innovative pharmaceutical industry and non-commercial trialists are currently prevented from conducting clinical trials of new medicines for emergency care on minors in the UK yet they can conduct them in other EEA countries.

The EU Directive On Clinical Research: Present Status Of Implementation With Regard To The Incompetent Patient

Lemaire F, Bion J, Blanco J et al. ICM 2005 ; 31 : 476-9

Country	Drug research only	Emergency research consent			
		Waiver	Deferred	Only if 'direct benefit'	Surrogate (LR) consent
Austria	Y	Y	Y	Y	Y
Belgium	No	Y	Y	No	Y
Czech R	Y	No	No	-	Y
France	No	Y	Y	No	Y
Germany	Y	Y	Y	Y	Y
Greece	Y	No	No	-	Y
Ireland	Y	N	N	-	Y
Italy	Y	Y	-	-	Y
NL	N	Y	Y	Y	Y
Norway		Y	Y	Y	Y
Portugal	Y	N	N	N	-
Spain	Y	Y	Y	N	Y
UK	N	*N*	*N*	*N*	Y

(b) The table above, published by the President of the European intensive care society, indicates that Austria, Belgium, France, Germany, Italy, Netherlands, Norway and Spain currently have provision for emergency care research while Czech R, Greece, Portugal and UK do not.

(c)The proposed amendment would remove this barrier to competition in the UK and thus encourage additional investment in R&D for emergency care medicines.

10. RESULT OF CONSULTATION

(i) Summary of responses to consultation document (MLX 340)

The consultation was circulated to over 2000 stakeholders and we received 52 responses from a range of organisations, including Primary Care Trusts, NHS Trusts, Research Ethics Committees, Royal Colleges, professional bodies and other bodies in the research sector. Of the 52 responses, 17 made no comment. There were no comments on the anticipated costs set out in the partial Regulatory Impact Assessment that accompanied the consultation letter. The vast majority of substantive responses supported the aims of the legislative amendments. A number of comments were made on the proposals, particularly on the need for clear and comprehensive guidance in respect of the new arrangements across all three areas.

(ii) Proposals to amend policy as a result of consultation

As a result of the responses to the consultation we propose to omit the original proposal to remove the review of gene therapy clinical trials for infectious disease from GTAC's remit

because the apparent ambiguity in the legal definition of “gene therapy” has now been resolved. Furthermore, the proposal received considerable resistance from the two main bodies concerned with gene therapy.

RECOMMENDATION

This impact assessment considers three options for implementing (a) an emergency care research amendment for minors, (b) changes to the role of the Gene Therapy Advisory Committee (GTAC) and (c) changes to the Committees, meetings and procedures for providing an ethical opinion:

Option 1 – Continue to rely on existing arrangements which would prevent (a) minors (children under 16 years) from participating in clinical trials of emergency care; (b) the GTAC from notifying UKECA that its advice is not required on routine gene therapy trials and for applications to be transferred to another recognised REC routine gene therapy applications; and (c) modification of the procedures for operation of RECs to widen the available expertise, reduce administrative procedures and rationalise the documents an applicant must submit for an opinion.

Option 2 – Interpret the current legislation in guidance which was shown to be impracticable because all the proposed changes are to requirements set out in the Regulations and cannot be implemented by guidance alone.

Option 3 – Implement the amendments to the Regulations to allow:

(a) minors to be entered into trials of medicines for emergency care without prior consent and fulfilling other current requirements. The use of the exception to the general requirement that informed consent must be obtained from a minor’s parents or legal representative prior to his/her participation in a trial would be subject to safeguards. First, the exception could only be relied on whilst it was not reasonably practicable to obtain consent. As soon as it became reasonable to obtain consent, that consent would be required. Second, the protocol under which the exception would be used must have prior approval of an ethics committee. The clinician who is providing emergency treatment related to the clinical trial would be provided with a detailed protocol – such as inclusion and exclusion criteria - that fully reflects the recommendations of the Ethics Committee that has approved the trial protocol. This would not increase the regulatory burden but benefit:

- **Minors who require emergency care by allowing them to participate in clinical trials of new treatments that might improve their prospects of recovery and survival;**
- **future minors by improving treatments for conditions that require emergency care;**
- **UK researchers by allowing them to participate in multinational trials of emergency care treatments;**
- **public health by providing the opportunity to reduce mortality and morbidity of children’s conditions requiring urgent treatment; and**
- **The pharmaceutical industry by allowing them to develop new essential medicines for emergency care of children as part of their business.**

(b) modification of the role of GTAC to allow GTAC to notify UKECA that its advice is not required on routine gene therapy trials and for applications to be transferred to another recognised REC for an opinion which will simplify procedures for sponsors conducting those type of trials and indirectly benefit those conducting complex gene therapy trials by providing GTAC more resource to consider them.

(c) modification of the procedures for operation of RECs to widen the available expertise, simplify the process and rationalise the documents an applicant must submit for an opinion which will indirectly benefit sponsors by improving the time a REC takes to

provide a final opinion and by reducing the documents that need to be submitted with an application for a REC opinion.

After careful consideration I recommend that the Government adopts the option to amend the Clinical Trials Regulations to allow (a) minors to be entered into trials of medicines for emergency care. (b) to allow GTAC to notify UKECA that its advice is not required on routine gene therapy trials and for applications to be transferred to another recognised REC for an opinion, and (c) modification of the procedures for operation of RECs to widen the available expertise, simplify the procedures and rationalise the documents an applicant must submit for an opinion.

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Specific Impact Tests: Checklist

Use the table below to demonstrate how broadly you have considered the potential impacts of your policy options.

Ensure that the results of any tests that impact on the cost-benefit analysis are contained within the main evidence base; other results may be annexed.

Type of testing undertaken	*Results in Evidence Base?*	*Results annexed?*
Competition Assessment	Yes	No
Small Firms Impact Test	Yes	No
Legal Aid	No	No
Sustainable Development	No	No
Carbon Assessment	No	No
Other Environment	No	No
Health Impact Assessment	No	No
Race Equality	No	No
Disability Equality	No	No
Gender Equality	No	No
Human Rights	No	No
Rural Proofing	No	No

Annexes

The policies recommended under Option 3 have been screened for their impact on race, disability and gender equality. There is no reason to believe that the policies will impact differently or discriminate unlawfully against people of different race or gender or people with disabilities. As the policies do not have any specific impact a full assessment is not necessary.