

# Emergency research and the interests of participants

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## Abstract

The UK Clinical Trials Regulations were amended in 2006 and 2008 to facilitate research on medicinal products administered in emergency situations. The Regulations, which implement the EU Clinical Trials Directive, had previously required prior consent to participation in a clinical trial from either the participant or the participant's legal representative. These amendments put emergency research on medicinal products on a similar footing to research on other types of invasive emergency treatment. This article argues that this was a positive development from the perspective of science and society and one for which there is a strong ethical basis. Nonetheless, it is argued that the UK Regulations cannot be interpreted consistently with European law without distortion contrary to the rule of law. It is also argued that the Directive needs to be amended or replaced to ensure a proper balance between the interests of participants and the interests of science and society. A number of specific suggestions are made, and the proposals made by the European Commission in July 2012 are supported. It is, however, argued that more needs to be done to protect the conduct of emergency trials from the conflicts of interests and biases that generally beset clinical trials.

## Keywords

Emergency research, medical research, Clinical Trials Directive, UK Clinical Trials Regulations, Mental Capacity Act

## Introduction

Informed consent has long been accepted as an important safeguard for protecting the interests of participants in medical research. Consent was declared to be 'absolutely essential' by the first principle of the 1947 Nuremberg Code<sup>1</sup> and this was only slightly qualified by the Helsinki Declaration of 1964 to permit research on an incapacitated patient with the approval of a legal representative.<sup>2</sup> It was not until the fifth revision of the Helsinki Declaration in 2000 that this was further modified to support research in an emergency situation where it is not possible to obtain consent from the participant or a proxy before entry into the trial.<sup>3</sup>

One of the largest trials of a new treatment in an emergency setting was the 'Thrombolysis in Cardiac Arrest (TROICA)' study, which sought to assess the safety and efficacy of administering the drug tenecteplase during cardiopulmonary resuscitation of

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<sup>1</sup> Reproduced as Appendix 1 to R. V. Carlson, K. M. Boyd, and D. J. Wedda, 'The revision of the Declaration of Helsinki: past, present and future', *British Journal of Clinical Pharmacology*, 57 (2004), p. 695.

<sup>2</sup> 1964 version, II.1. Reproduced in *Bulletin of World Health Organization* 86 (2008), p. 652.

<sup>3</sup> 2000 version, para. 26.

patients who had out-of-hospital cardiac arrest.<sup>4</sup> This double-blind, multi-centre trial involved patients being given standard resuscitation with either tenecteplase or a placebo. This appears to have been a paradigmatic instance of a trial designed to resolve genuine clinical uncertainty over a new treatment for which it was not feasible to obtain the prior informed consent of the participants. It actually established a negative—this trial was ended prematurely after the results of the first 1000 patients detected no significant differences between the tenecteplase and placebo groups.<sup>5</sup> Some clinical trials taking place in emergency settings have produced significant positive findings.<sup>6</sup>

This article considers the legal and ethical issues raised by research into emergency treatment for which prior informed consent is not feasible. This potentially concerns attempts to test the safety and efficacy of treatments in a wide range of sudden, incapacitating emergency situations. Such emergency situations could be created by, for example, cardiac arrest, severe stroke, anaphylactic shock, severe head injuries, or severed arteries. The United Kingdom has two closely related regulatory frameworks addressing emergency research of this type, depending on whether or not the trial involves the testing of a new medicinal product. This article examines both. It begins by examining emergency research involving medicinal products, arguing that the UK's approach is at odds with European law. It is argued that future amendment or repeal of the EU Clinical Trials Directive (2001/20/EC) needs to rebalance the interests of research participants with others' interests. A number of specific suggestions are made in this article as to the nature of this rebalancing and, in the process, support is offered for the proposals made by the European Commission in July 2012. Nonetheless, it is argued, that further consideration needs to be given to trialling a more radical proposal.

This article has four sections. The first analyses the UK's regulatory approach towards emergency research involving medicinal products. It is shown that, in contrast to the UK's approach and that of various international instruments, the Directive's provisions leave no flexibility for defensibly dispensing with the need for prior consent before undertaking emergency research. In the second section, analysis of the UK's regulatory position towards emergency research not involving medicinal products reveals a different approach to the interests of participants. The consequences of the regulatory distinction drawn between emergency research on children and on incapacitated adults are shown to contrast with the approach adopted by the Directive. The third section directly addresses the Directive's adoption of the principle that the interests of the patient should always prevail over those of science and society. This principle is applied in the first section and shown in the second section to more closely reflect the Directive's approach to incapacitated adults than to children. In the third section, this principle is shown to raise conceptual problems. The fourth section advances the view that many of the problems that generally beset clinical trials have particular relevance in the absence of the safeguard of informed consent, so extra care needs to be taken to ensure transparency, maximisation of the benefits of emergency trials, and the minimisation of factors that artificially magnify or protect the interests of persons other than the participant. Therefore, it is argued, there is an ethical case for trialling the radical response of centralising control over the design and implementation of emergency trials.

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<sup>4</sup> F. Spöhr and others, 'International Multicentre Trial Protocol to Assess the Efficacy and Safety of Tenecteplase during Cardiopulmonary Resuscitation in Patients with Out-of-Hospital Cardiac Arrest: The Thrombolysis in Cardiac Arrest (TROICA) Study', *European Journal of Clinical Investigation*, 35 (2005), p. 315.

<sup>5</sup> Böttiger, B.W. and others, 'Thrombolysis during Resuscitation for Out-of-Hospital Cardiac Arrest', *New England Journal of Medicine*, 359 (2008), p. 2651.

<sup>6</sup> See, for example, CRASH trial collaborators, 'Final results of MRC CRASH, a randomised placebo-controlled trial of intravenous corticosteroids in adults with head injury—outcomes at 6 months', *Lancet*, 365 (2005), pp. 1957–59 and CRASH2, <http://crash2.lshtm.ac.uk> (accessed 22 June 2012).

## The regulation of emergency trials using medicinal products

Clinical trials on medicinal products are regulated in the United Kingdom by a set of Regulations enacted in 2004 and subsequently amended: the Medicines for Human Use (Clinical Trials) Regulations 2004/1031 (hereafter referred to as the Clinical Trials Regulations). The amended Regulations are intended to give full effect to two EU Directives: the Clinical Trials Directive and the Good Clinical Practice (GCP) Directive (2005/28/EC).

The Clinical Trials Regulations, like the EU legislation that they implement, require a number of conditions to be satisfied before a person is entered into a clinical trial of a medicinal product that is either under development or used outside of its market authorisation.<sup>7</sup> One of these conditions is that those who are entered into a clinical trial or their legal representatives must have given informed consent.<sup>8</sup> Amendments introduced an exception to these conditions with regard to adults in 2006 (by Regulations 2006/2984) and with regard to children in 2008 (by Regulations 2008/941). Thus, there is now an exception to the need for prior consent where:

1. treatment is required urgently;
2. the nature of the trial requires urgent action;
3. it is not reasonably practicable to meet the relevant conditions of Schedule 1 of the Regulations; and
4. the procedure adopted has received prior approval from an ethics committee.<sup>9</sup>

This exception could clearly capture a trial like that of the TROICA study. Such a departure from the cornerstone of prior informed consent is supported by the International Committee on Harmonization (ICH) Guidance for Good Clinical Practice 1995<sup>10</sup> and by the 2000 and 2008 versions of the Helsinki Declaration.

The ICH guidance states that prior consent should be obtained if possible, but, when it is not possible, the enrolment of the participant should comply with the protocol and the applicable regulatory requirements, and have received prior approval from an ethics committee. Further, the participant or the participant's legal representative should be informed about the trial as soon as possible and consent to continue should be requested. This guidance, therefore, envisages permissive national regulatory requirements of the type now enacted by the United Kingdom.

Paragraph 29 of the 2008 version of the Helsinki Declaration states that research on those incapable of giving consent, such as unconscious patients, may be performed without prior consent where four conditions are satisfied. These are:

- a. the physical or mental condition that prevents the giving of informed consent is a necessary characteristic of the research population;
- b. no legal representative is available and the research cannot be delayed;
- c. the specific reasons for using such participants have been stated in the research protocol and the study has been approved by a research ethics committee; and

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<sup>7</sup> Reg. 2 ('investigational medicinal products').

<sup>8</sup> Sch.1, Part 3, para 3 (adults able to consent or who have given consent prior to incapacity); Part 4, para. 4 (children); and Part 5, para.4 (incapacitated adults).

<sup>9</sup> Sch.1, Part 1, para 1(6)–(7).

<sup>10</sup> paras 3.1.7 and 4.8.15. See <http://ichgcp.net> (accessed 22 June 2012).

- d. consent to remain in the research should be obtained as soon as possible from the participant or legal representative.

These four conditions are more specific than those in the ICH guidance and the first three present similar safeguards to the above listed 1–4 conditions of the UK Regulations. There is no direct equivalent of condition d, which is also a condition of the ICH guidance, in the four conditions of the Clinical Trials Regulations outlined above. Nonetheless, this could be considered to be implied by statements elsewhere in the Regulations to the effect that a participant with capacity, or the legal representative of a participant who lacks capacity, may withdraw from the trial at any time.<sup>11</sup>

The problem, however, is that the EU legislation that the Clinical Trials Regulations purport to implement does not contain an explicit exception to the need to obtain prior consent of the type expressed in the ICH guidance or the Helsinki Declaration. Article 3 of the Clinical Trials Directive states that the trial may only be undertaken if the participant or the legal representative ‘has had the opportunity, in a *prior* interview...to understand the objectives, risks and inconveniences of the trial’ and ‘has given his...consent after being informed of the nature, significance, implications and risks of the clinical trial’ (emphasis added). The past tense is similarly invoked by the Directive’s statement that a trial on children<sup>12</sup> or adults who are not able to consent<sup>13</sup> may only be undertaken if the informed consent of the legal representative ‘has been obtained’. And, if this were in any doubt, recital 4 of the Directive declares that where the trial is to involve persons incapable of giving their consent, the written consent of their legal representative is necessary ‘before participation in any such clinical trial’.

#### *Dispensing with informed consent within the Directive*

Given the endorsement of the view that the requirement to obtain *prior* consent is not an absolute ethical requirement by the ICH guidance of 1995 and by the 2000 and 2008 versions of the Helsinki Declaration, can we not simply read an exception into the Directive’s apparently absolute requirement? Such an approach was suggested by the Medicines and Healthcare products Regulatory Agency (MHRA) in its 2005 consultation on the UK Regulations.<sup>14</sup> But, if this is to be a defensible interpretation of the legislation, it must at least be consistent with its provisions and fundamental principles.

As was suggested by the MHRA,<sup>15</sup> the ICH guidance and the Helsinki Declaration are relevant to the principles of the Directive. Recital 6 of the Clinical Trials Directive cites the ICH as an example of ‘appropriate fora’ for pursuing the harmonisation of the technical requirements for the development of medicinal products and recital 8 of the GCP Directive declares that the ICH guidance should be ‘taken into account’. Similarly, recital 2 of the Clinical Trials Directive and Article 3 of the GCP Directive requires clinical trials to be conducted ‘in accordance’ with the Declaration of Helsinki. These provisions are, however, not as supportive of an implied qualification to the need for prior consent as they first appear.

The reference to the prior ICH guidance enables it to be taken into account, but this is not the same thing as treating the guidance as decisively laying down the goals of the Directive so as to permit departure from its clearly worded provisions. The references to the ICH

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<sup>11</sup> Sch.1, Part 3, para 2; Part 4, para 3; and Part 5, para 3.

<sup>12</sup> Article 4(a).

<sup>13</sup> Article 5(a).

<sup>14</sup> MHRA, Consultation on Amendment to the Medicines for Human Use (Clinical Trials) Regulations 2004 (S.I. 2004/1031). MLX 326. 1 August 2005, at para 9.

<sup>15</sup> MHRA, ‘Consultation on Amendment’.

guidance in the recitals of the EU legislation are not sufficient to support deference to the guidance where it conflicts with the Articles of the Clinical Trials Directive.

The reference to the Helsinki Declaration goes further, but it is explicitly a reference to the 1996 version of the Declaration, which contained no provision for emergency research without prior consent. Indeed, paragraph 11 of that version of the Declaration requires the consent of the participant, providing for exception only in the following narrow terms: ‘Where physical or mental incapacity makes it impossible to obtain informed consent, or when the subject is a minor, permission from the responsible relative replaces that of the subject in accordance with national legislation’. Further, a key provision of the 1996 version of the Helsinki Declaration asserts that ‘Concern for the interests of the subject *must always prevail* over the interests of science and society’.<sup>16</sup> This is given effect by Articles 4(i) and 5(h) of the Clinical Trials Directive, which provide that it is a condition of clinical trials on children and incapacitated adults that ‘the interests of the patient *always prevail* over those of science and society’.<sup>17</sup> Interpreting these provisions as consistent with the legislation as a whole<sup>18</sup> requires that priority be given to the interests of child and incapacitated adult patients, unless otherwise stated or implied by the legislation.

Dispensing with prior consent makes it possible to conduct some types of research in an emergency setting that would not otherwise be able to take place, and thereby advances the interests of science and society. But does it advance, or at least not weaken, the protection given to the interests of participants? This question is important, because, if it does not, then it cannot be permissible to interpret the Directive so as to read in an exception to the prior consent requirement, because to do so would be to ignore Articles 4(i) and 5(h).

In order to answer this question, we will consider the situation where there is scientific uncertainty over which of two treatments is better to administer in an emergency setting.<sup>19</sup> In such a situation, the choice is between simply treating patients and conducting research to resolve the uncertainty. Thus, the options are:

- (1) the health care professional administering whichever treatment he or she believes to be better without research-related procedures,
- (2) entering the patient into a trial (in which one of these treatments is randomly chosen for administration) without consent/consultation, or
- (3) entering the patient into a trial with consent/consultation.

Option 1 is simply emergency treatment and, as such, the health care professional is only concerned with that patient’s therapeutic needs. Options 2 and 3 involve emergency research aimed at producing generalisable knowledge and thereby involving the collection of information and the application of procedures beyond those directed to the patient’s therapeutic needs.<sup>20</sup> In an emergency situation, it is generally neither feasible nor in the interests of patients to pursue option 3 by delaying treatment to consult with the patient or the patient’s proxy. This is because such treatments generally involve a narrow ‘therapeutic

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<sup>16</sup> Declaration of Helsinki, 1996 version, I.5 (emphasis added).

<sup>17</sup> Emphasis added.

<sup>18</sup> In the 2008 version of the Declaration of Helsinki, which has a variant of this principle, the very first paragraph states that the Declaration is to be ‘read as a whole’ and each paragraph ‘should not be applied without consideration of all other relevant paragraphs’. Such an approach to any instrument is surely required if it is to be interpreted coherently.

<sup>19</sup> See the discussion of ‘clinical equipoise’.

<sup>20</sup> Common non-therapeutic interventions in emergency research include physical examinations, venepunctures, and review of medical records: see A. D. McRae and C. Weijer, ‘Lessons from Everyday Lives: A Moral Justification for Acute Care Research’, *Critical Care Medicine*, 30 (2002), pp.1146, 1148–1149.

window'.<sup>21</sup> For example, one study has shown that in the early stages of out-of-hospital cardiac arrest every minute of delay in providing defibrillation reduces the survival rate by over 20%.<sup>22</sup> However, strictly treating the interests of the patient as always prevalent would favour option 1, because only that option is solely concerned with the patient's therapeutic interests. The patient may have (non-therapeutic) interests that are opposed to departing from option 1, such as where the patient has previously expressed values or beliefs rejecting participation in research, or the additional tests and data collection that the research requires. Thus, treating the interests of the patient as prevalent does not support dispensing with prior informed consent so as to enter a patient into a clinical trial. Even if it did, the Directive's invocation of this principle would not be a sufficient justification for reading an exception into the requirement to obtain prior informed consent. It is one thing to use a principle of the Directive to elaborate on matters left unaddressed or insufficiently detailed, and quite another to use it to override unambiguous provisions.

Between October 2009 and January 2010, the European Commission ran a public consultation on the operation of the Clinical Trials Directive.<sup>23</sup> The consultation document noted that the information that needs to be provided prior to obtaining informed consent is 'extensive, covering several pages and lasting up to two hours'.<sup>24</sup> It also noted that between the Directive coming into force on 1 May 2004 and the consultation, applications had been made for 532 emergency clinical trials to take place. It went on to state that, 'This situation is not addressed in the rules for obtaining informed consent in the Clinical Trials Directive'.<sup>25</sup> This implicitly concedes that the prior consent requirement is an absolute requirement in the Directive. Despite this, 10 European Union countries have legislation permitting emergency research without prior consent.<sup>26</sup> These countries are either in contravention of EU law or the Directive is to be interpreted contrary to its expressed terms and, as argued above, its principles. As indicated above, the MHRA took a different view when it sought amendment of the Clinical Trials Regulations to permit emergency research without prior consent.<sup>27</sup> According to its 2005 consultation,

Whilst there are no specific provisions in the Directive allowing an exception from the general requirement of prior consent, we consider that the proposed exception is within the spirit of the Directive.<sup>28</sup>

But, if the analysis above is sound, such an approach to the terms of the Directive involves the adoption of an unacceptable legal fiction.<sup>29</sup> Lon Fuller has convincingly argued that the Rule of Law requires that the rules be non-contradictory and that there should be congruence between official action and declared rule.<sup>30</sup> If the Directive is to be interpreted to permit an exception to prior consent on the basis that obtaining such consent is not feasible in an

<sup>21</sup> McRae and Weijer, 'Lessons from Everyday', at p. 1146.

<sup>22</sup> V. J. De Maio et al. 'Optimal Defibrillation Response Intervals for Maximum Out-of-Hospital Cardiac Arrest Survival Rates', *Annals of Emergency Medicine*, 42 (2003), p. 242, 247.

<sup>23</sup> European Commission, 'Assessment of the Functioning of the 'Clinical Trials Directive' 2001/20/EC: Public Consultation Paper'. Brussels, 09/10/2009. ENTR?F/SF D(2009) 32674.

<sup>24</sup> 'European Commission', p. 24.

<sup>25</sup> 'European Commission', p. 25.

<sup>26</sup> 'European Commission', p. 25.

<sup>27</sup> MHRA, 'Consultation on Amendment'.

<sup>28</sup> 'Consultation on Amendment', para 9.

<sup>29</sup> On the proper and improper use of legal fictions see M. Adcock and D. Beyleveld, 'Purposive interpretation and the regulation of technology: legal constructs, legal fictions, and the rule of law', *Medical Law International*, 8(4) (2007), p. 305.

<sup>30</sup> L. Fuller, *The Morality of Law*, 2nd ed. (New Haven, CT: Yale University Press, 1969), at pp. 65–70 81–91.

emergency setting, then the Directive is self-contradictory and there is incongruence between the declared rule and how it is applied.

The European Commission's consultation document advanced the view that 'it should be a serious setback for clinical research if medicinal research in emergency situations proved to be impossible in Europe'. This is indeed true and such research is required to ensure that medical knowledge and treatment continues to advance.<sup>31</sup> But it is a serious setback to the rule of law if inconvenient and unduly restrictive legislation may be ignored or given fictionalised interpretations. The better approach is to seek to accelerate its amendment or replacement.

The responses to the public consultation, published in February 2010, indicated that most accepted that the situation under the Clinical Trials Directive was 'unsatisfactory'.<sup>32</sup> The Commission issued a further consultation in February 2011<sup>33</sup> and, in July 2012, issued a draft regulation that it hopes will replace the Directive by 2016.<sup>34</sup> This draft regulation proposes to dispense with prior consent in specified circumstances (to be examined in the course of the next section). It proposes to re-enact various other provisions, including a slightly reformulated version of the prevalence principle, which will be examined in the section entitled 'The rights and interests of the participant'.

### **Emergency trials of other types of invasive treatment, and the interests of incapacitated adults versus children**

Emergency research need not involve the testing of a medicinal product and, if it does not, it will fall outside of the Clinical Trials Directive and the implementing Clinical Trials Regulations. For example, consider a research trial of alternative cardio-pulmonary resuscitation techniques for heart attack victims.<sup>35</sup> In England and Wales, such trials would need to comply with the requirements of the common law (in the case of children) or the Mental Capacity Act 2005 (in the case of those who are older than 16 years and lack capacity).<sup>36</sup> The 2005 Act is also important to the application of the Clinical Trials Regulations to emergency research, because those Regulations do not specify when an adult<sup>37</sup> is to be regarded as 'unable by virtue of physical or mental incapacity to give informed consent'.<sup>38</sup> Adult patients are to be regarded as incapacitated when they fail to satisfy the two-stage capacity test in the 2005 Act.<sup>39</sup>

Below it will be shown that the differences between the common law and the 2005 Act have significance for the lawfulness of emergency research and the result is that emergency research on children is far more problematic than emergency research on incapacitated adults. This approach will be contrasted with that adopted by the Clinical Trials

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<sup>31</sup> There is, for example, a dearth of clinical trials in trauma care: I. Roberts et al. 'Trauma care research and the war on uncertainty', *British Medical Journal*, 331 (2005), p. 1094.

<sup>32</sup> European Commission, 'Assessment of the Function of the 'Clinical Trials Directive' 2001/20/EC: Summary of Responses to the Public Consultation Paper'. Brussels, 20 March 2010. SanCO/C/8/SF/dn D(2010) 380240, p. 14.

<sup>33</sup> European Commission, *Revision of the 'Clinical Trials Directive' 2001/20/EC: Concept Paper Submitted for Public Consultation*. Brussels, 9 February 2011, SANC/C/8/PB/SF D(2011) 143488.

<sup>34</sup> European Commission, *Proposal for a Regulation of the European Parliament and the Council on Clinical Trials on Medicinal Products for Human use, and Repealing Directive 2001/20/EC*. Brussels, 17 July 2012. CoM (2012) 369 final.

<sup>35</sup> See A. Hallstrom et al. 'Cardiopulmonary Resuscitation by Chest Compression Alone or with Mouth-to-Mouth Ventilation' *New England Journal of Medicine*, 342 (2000), pp. 1546–1553.

<sup>36</sup> In Scotland, the Adults with Incapacity (Scotland) Act 2000 applies to those 16 or over (s. 1(6)).

<sup>37</sup> Defined as someone who has attained the age of 16 years: Reg. 2(1).

<sup>38</sup> Sch. 1, para 1(4)9a)

<sup>39</sup> Ss.2 and 3, which are to be read in the light of the s. 1 principles.

Regulations, which reproduce regulatory differences between children and incapacitated adults from the Directive that are, it will be argued, inappropriate in the context of emergency research. It will be further argued that the EU Regulation proposed by the European Commission offers a more coherent approach than that currently adopted by the UK Regulations.

### *Research on children*

The common law position on research involving children is largely a matter of supposition, because of the paucity of case law. Outside of an emergency context, it is even unclear whether a researcher may rely on the consent of a child, because the legislation that permits the consent of 16 year old children to be regarded as an adult's only applies to therapeutic and diagnostic procedures<sup>40</sup> and there is doubt on whether it is possible to rely on satisfaction of the *Gillick* test.<sup>41</sup> In an emergency setting, healthcare professionals may undoubtedly treat a child without the authorising consent of the child or parent,<sup>42</sup> but there is no common law support for extending this to research. The Royal College of Paediatrics has opined that, provided that the project as a whole has been approved by an ethics committee, 'it would be ethical to carry out research on children on such occasions of extreme urgency without obtaining consent'.<sup>43</sup> It went on to accept that it is 'possible' that this would still be unlawful. With respect, this is more than a mere possibility, because the emergency exception as addressed in the case law is articulated as tracking the interests of the child. In *Gillick*, Lord Templeman expressed it thus:

I accept that if there is no time to obtain a decision from the court, a doctor may safely carry out treatment in an emergency if the doctor believes the treatment to be *vital to the survival or health of an infant* and notwithstanding the opposition of a parent or the impossibility of alerting the parent before the treatment is carried out. In such a case the doctor must have the courage of his convictions that the treatment is necessary and urgent *in the interests of the patient*...<sup>44</sup>

Thus, invasive research without prior consent on children is probably unlawful in England and Wales, unless the research falls within the Clinical Trials Regulations or the Mental Capacity Act (which does not apply to those under 16).

### *The conditions applying to research under the Mental Capacity Act 2005*

The 2005 Act has specific provisions dealing with research on incapacitated adults to which the Clinical Trials Regulations do not apply.<sup>45</sup> Such intrusive research must be part of a

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<sup>40</sup> See s. 8(1) of the Family Law Reform Act 1969 and *Re W* [1993] Fam. 64, pp. 78 and 92. Compare: Royal College of Paediatrics and Child Health, 'Ethics Advisory Committee Guidelines for the Ethical Conduct of Medical Research involving Children', *Archives of Disease in Childhood*, 82 (2000), p. 177, 180.

<sup>41</sup> *Gillick v West Norfolk and Wisbech AHA* [1986] A.C. 112 did not consider research and obiter in *Re W* [1993] Fam. 64, esp. p.78 expresses doubt about whether the consent of a child could authorise a serious non-therapeutic procedure that does not benefit that child.

<sup>42</sup> *Gillick* [1986] A.C. 112, pp. 138, 181–182, 189, 200, 204. See also Children Act 1989, s. 3(5), which empowers those who have 'care of the child' but lack parental responsibility to do what is 'reasonable' to protect the child's welfare.

<sup>43</sup> College of Paediatrics and Child Health, n. 40 above, at p. 180.

<sup>44</sup> *Gillick* [1986] A.C. 112, p. 180. Emphasis added.

<sup>45</sup> Ss 30 to 34.

protocol approved by a research ethics committee (REC).<sup>46</sup> The REC must be satisfied that the research relates to the participant's 'impairing condition' or its treatment,<sup>47</sup> and that there are reasonable grounds for believing that the research cannot be done as effectively using those who have capacity.<sup>48</sup> The REC must also be satisfied that the benefits justify the research in one of two ways. The first is where the research has the potential to benefit the participant without imposing on that person any burden disproportionate to the potential benefit.<sup>49</sup> The alternative is where the research is intended to provide knowledge that will benefit those affected by the same or a similar condition, where there are reasonable grounds for believing that the risks to the participant are 'negligible', and the research will not significantly interfere with the participant's freedom or privacy, or be unduly invasive or restrictive.<sup>50</sup>

Some of the conditions imposed by the 2005 Act with regard to incapacitated adults differ from those imposed by the Clinical Trials Directive and the UK Regulations. The first condition is essentially similar to Article 5 of the Directive, which requires that the research be essential to validate data obtained in clinical trials on capacitated persons and relate directly to a life-threatening or debilitating clinical condition from which the incapacitated adult suffers.<sup>51</sup> The two grounds addressing the benefits of the research differ more significantly. The Directive requires that 'there be grounds for expecting that administering the medicinal product to be tested will produce a benefit to the patient outweighing the risks or produce no risks at all'.<sup>52</sup> Thus, the second arm in the Directive refers to there being 'no risks at all' to the participant, whereas the 2005 Act is satisfied by the risks merely being 'negligible'. This variation in degree is potentially significant. Interestingly, the Directive is far more permissive with regard to research on children than either it or the 2005 Act are with regard to incapacitated adults. With regard to children, Article 4 of the Directive provides that there must be some direct benefit to the group of participants involved in the trial, the research must be essential to validate data obtained in clinical trials on capacitated persons, and the research must either relate directly to a condition from which the child participant suffers or only be capable of being carried out on children.<sup>53</sup> Thus, for adults the research must be therapeutic or carry no/negligible risks to the participant, whereas for children the Directive only requires that the research benefit *the group* of participants as a whole *and it does not require that the risks be non-existent or negligible*.<sup>54</sup>

The approach of the Clinical Trials Directive to research on children contrasts with that of the European Convention on Human Rights and Biomedicine, on which the research provisions of the Mental Capacity Act are based.<sup>55</sup> The Biomedicine Convention does permit research that is not expected to directly benefit the health of a participant who is unable to consent, but only 'exceptionally' where it is intended to benefit those with the participant's condition or persons in the same age category, and entails only minimal risk and minimal

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<sup>46</sup> S. 30(1).

<sup>47</sup> S. 31(2)/(3). The 'impairing condition' to which the research must relate under the 2005 Act is defined as a condition attributable to, causing, or contributing to the impairment or disturbance in the functioning of the participant's mind or brain.

<sup>48</sup> S. 31(4).

<sup>49</sup> S. 31(5)(a).

<sup>50</sup> S. 31(5)(b) and (6).

<sup>51</sup> Article 5(e) and Sch.1, Part 5, paras 10 and 11 of the Clinical Trials Regulations.

<sup>52</sup> Article 5(i) and Sch.1, Part 5, para 9 of the Clinical Trials Regulations.

<sup>53</sup> Article 4(e) and Sch.1, Part 4, para 9 of the Clinical Trials Regulations.

<sup>54</sup> It should be noted that, whether the trial is conducted on an incapacitated adult or a child, it must 'have been designed to minimise pain, discomfort, fear or other foreseeable risk in relation to the disease and its development stage' (Articles 4(g) and 5(f)).

<sup>55</sup> See para 96 of the Explanatory Notes to the 2005 Act.

burden to the participant.<sup>56</sup> Why does the Clinical Trials Directive have more permissive conditions for entering children into a research project? The European Commission has noted that it is particularly important that research takes place on children because they are not, biologically speaking, small adults and more than 50% of medicines used to treat children have not actually been tested on children.<sup>57</sup> To this end, the European Union has enacted further legislation to encourage research on medicinal products for paediatric use.<sup>58</sup> It is certainly the case that phase 1 trials of new medicinal products—i.e. small group trials of the safety and side effects of a new drug—can only take place on young children if it is permissible to rely on a benefit to the group of such child participants as a whole and permissible for the child participant to face a non-negligible risk. In contrast, many phase 1 trials on adults may enrol adults who are able to consent and there is therefore no need to enrol incapacitated adults in such trials. But once we are testing a medicinal product in an emergency setting for which obtaining the prior consent of any participant is not feasible, it is necessary to test new drugs on both children and incapacitated adults. I therefore contend that, *for research in an emergency setting*, the conditions applying to the two groups should be consistent. This is not the approach adopted by the UK's Clinical Trials Regulations, which have retained the conditions of the Directive specifying the risk/benefit requirements for research on children and incapacitated adults. The point is that, in an emergency context, there is no rationale for making the conditions for enrolling a child easier to satisfy than the conditions for enrolling an adult; and the distinction therefore cannot defensibly apply to emergency trials.

The EU Regulation proposed by the European Commission as a replacement for the Directive adopts a different approach than that of the UK Regulations. One of the conditions laid down for dispensing with prior consent in emergency situations by the draft Regulation is that 'the clinical trial poses a minimal risk to, and imposes a minimal burden on, the subject'.<sup>59</sup> This fully addresses the points made above and will bring the EU legislation in line with the Biomedicine Convention's approach to emergency research.

#### *Other conditions applying to emergency research*

In addition to the conditions outlined above, the 2005 Act requires researchers to consult with the participant's carer or, if the researcher is unable to identify such a person after taking reasonable steps to do so, a nominated independent person.<sup>60</sup> This consultation is to take place before the start of the trial,<sup>61</sup> and the participant is not to be entered into the trial if the person consulted advises that the participant's wishes and feelings would be likely to have led him or her to decline to take part in the project. If applied strictly, this consultation requirement would effectively prevent emergency research of the type considered in this article, but the Act does provide for an exception. The exception applies where urgent treatment is provided and the researcher considers it necessary to take action for the purposes of the research as a matter of urgency and not reasonably practicable to consult.<sup>62</sup> The researcher must also have the agreement of an independent doctor or, where that is not reasonably practicable, the protocol to this effect must have been approved by an REC.<sup>63</sup> The

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<sup>56</sup> Article 17(2).

<sup>57</sup> See European Commission, *'Proposed Regulation on Medicinal Products for Paediatric Use: Overview and Explanation of the Proposal'* (2004), p. 1.

<sup>58</sup> EU Regulation 1901/2006 on medicinal products for paediatric use.

<sup>59</sup> Article 32(1)(e).

<sup>60</sup> S. 32.

<sup>61</sup> Implied by the wording of s. 32(1)(b).

<sup>62</sup> S. 32(8).

<sup>63</sup> S. 32(9).

procedure for dispensing with prior consultation is thus very similar to that in the Clinical Trials Regulations for dispensing with prior informed consent. The essential difference is the reference to the agreement of an independent doctor, as there is no such procedure offered as an alternative to prior informed consent in the UK Regulations. There is similarly no such additional procedure proposed for the draft EU Regulation.

The Mental Capacity Act 2005 does not apply to Scotland, but the Adults with Incapacity (Scotland) Act 2000 has very similar provisions addressing emergency research. This Act generally requires the consent of the guardian or welfare attorney, or the adult's nearest relative.<sup>64</sup> An exception applies where it is not practicable to contact such a person before entry into the trial, and consent has been obtained from either the participant's doctor or a nominated independent person.<sup>65</sup> A further exception applies where it is not reasonably practicable to obtain the consent of any of these persons where: the treatment provided in the research is a matter of urgency, it is necessary to take action for the purposes of the research as a matter of urgency, and the research has been approved by a research ethics committee.<sup>66</sup> Like the Mental Capacity Act, the Scottish Act provides for an additional situation between those in which it is possible to get the prior consent of a proxy and situations in which it is not possible to consult with or get consent from persons outside of the trial.

The EU Regulation proposed by the European Commission permits research where the urgency of the situation, caused by a sudden serious medical condition, makes it impossible to obtain prior informed consent.<sup>67</sup> The participant must not have previously expressed objections known to the researcher and informed consent must be obtained as soon as possible.

Once the EU Regulation is in force, the United Kingdom will have a coherent approach to emergency research involving medicinal products and emergency research falling within the 2005 Act. Further legislative intervention, or judicial development of the common law, will be required to bring emergency research on children that does not involve medicinal products in line with these developments.

## **The rights and interests of the participant**

The earlier analysis of the Clinical Trials Directive addressed its adoption of the principle that the interests of 'the patient' should 'always prevail' over those of science and society. The 2005 Act similarly declares in relation to research on incapacitated adults falling within its provisions that '[t]he interests of the person must be assumed to outweigh those of science and society'.<sup>68</sup> This principle, being so central to the regulatory frameworks considered above, stands in need of analysis. It will be argued that this principle raises conceptual difficulties and the formulation in the draft EU Regulation is to be preferred.

The above principle has its origins in the Declaration of Helsinki and has been expressed slightly differently in the various versions of that instrument. Its initial appearance as a declared principle was in the first revision of the Helsinki Declaration in 1975, where it appeared twice.<sup>69</sup> It appeared as a basic principle ('Concern for the interests of the subject must always prevail over the interests of science and society')<sup>70</sup> and as a principle of non-therapeutic research ('In research on man, the interest of science and society should never

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<sup>64</sup> S. 51(3)(f).

<sup>65</sup> S. 51(3A)(b).

<sup>66</sup> S. 51(3A)(c).

<sup>67</sup> Article 32.

<sup>68</sup> S. 32(3).

<sup>69</sup> This version of the Declaration is reproduced as Appendix 2 in Carlson et al, 'Declaration of Helsinki'.  
<sup>70</sup> Declaration of Helsinki, 1975 version, I.6.

take precedence over considerations related to the well-being of the subject'.<sup>71</sup> The wording of these statements remained unchanged through revisions of the Declaration in 1983, 1989, and 1996. These were reduced to a single provision in the fifth revision in 2000: 'In medical research on human subjects, considerations related to the well-being of the human subject should take precedence over the interests of science and society'.<sup>72</sup> In the latest version of the Declaration, adopted by the World Medical Association in 2008, this became: 'In medical research involving human subjects, the well-being of the individual research subject must take precedence over all other interests'.<sup>73</sup> Thus, the Helsinki Declaration no longer declares that *all the interests* of the participant should *always prevail* over the *interests of science and society*. Now, it simply requires that the *well-being* of the participant must take *precedence* over *all other interests*. This is potentially a significant evolution of the principle, but there is also shared essence between these formulations.

The principle in all of its formulations is clearly deontological in the sense that it does not permit the aggregation of the rights or interests of others to outweigh a more important right or interest possessed by the participant. The principle, as it was originally expressed in the Helsinki Declaration and remains expressed in the Clinical Trials Directive, does not permit the interests of the individual participant to be outweighed by the collective interests of science and society. The principle as it is now formulated in the Helsinki Declaration does not permit the well-being of the individual participant to be outweighed by collective interests of any type. This aspect of the principle is significant because the combined collective interests favouring entry of a person into a clinical trial could be considerable. The interests of persons other than the participant include the interests of researchers (it should not be forgotten that career progression and prestige often track research outcomes and publications),<sup>74</sup> the company producing the new treatment to be trialled,<sup>75</sup> future patients, and the scientific community.

The characterisation of a principle or theory as deontological is often misunderstood. Consider, for example, the view advanced by McCarthy that,

Those who subscribe to one or another of the deontological theories of ethics that draw inspiration from Immanuel Kant...contend that it is always and everywhere wrong to 'use' human subjects without their informed consent.<sup>76</sup>

If this were correct, then deontological theories of ethics would have to reject all research on those unable to give their informed consent, whether or not it takes place in an emergency setting. But, while such a view is advocated by some deontological theorists,<sup>77</sup> it is not implied by the fact that the theory is deontological in the sense defined above. Deontological

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<sup>71</sup> 1975 version, III.4.

<sup>72</sup> This version of the Declaration is reproduced as Appendix 3 in Carlson, et al. 'Declaration of Helsinki'.

<sup>73</sup> Para 6. Available at: <http://www.wma.net/en/30publications/10policies/b3/> (accessed 22 June 2012).

<sup>74</sup> See also N. G. Levinsky, 'Nonfinancial Conflicts of Interest in Research', *New England Journal of Medicine*, 347 (2002), p. 759.

<sup>75</sup> A meta-study by Morgan et al. ('The Cost of Drug Development: A Systematic Review', *Health Policy*, 100 (2011), p. 4) indicates that the cost of drug development ranged from US\$92m to US\$83.6m for out-of-pocket expenses, with much greater costs if the estimates include the capitalised cost.

<sup>76</sup> C.B. McCarthy, 'Editorial: Ethical Considerations of New Guidelines for Emergency Research', *American Journal of Respiratory and Critical Care Medicine*, 153 (1996), p. 507, at p. 507.

<sup>77</sup> For example, P. Ramsey, 'The Enforcement of Morals: Nontherapeutic Research on Children', *Hastings Center Report*, 6(4) (1976), p. 21.

theories need not consider the rights/interests<sup>78</sup> of a participant to outweigh any possible right or interest of any other, so that it is only permissible to enter a participant into a clinical trial where that person has waived the benefit of the relevant rights/interests by consenting.<sup>79</sup> This is for two reasons. First, it does not automatically follow from the characterisation of a theory as deontological that it holds that all human participants in a clinical trial have equal rights and interests. The principle in the Helsinki Declaration *does* imply that all human participants have equal rights/interests, but other deontological positions could coherently hold that the rights/interests of some participants (typically, the permanently cognitively enfeebled) are sometimes less weighty than the rights of other participants.<sup>80</sup> Secondly, the characterisation of a theory as deontological does not imply that a right/interest of an individual participant can never be overridden by a more important right/interest of another individual. To hold that the individual's consent is the only permissible justification for participation in a clinical trial is to hold that others can never have more important conflicting rights, which implies that *either* research participants are a special category of person with greater rights/interests than members of other groups *or* the participant's most important rights/interests are always violated by non-consensual participation in a clinical trial. The first of these alternatives would be misguided because participating in research does not magnify an individual's intrinsic moral status; an individual does not get more rights or more important rights by dint of entry into a trial. The second is too encompassing because participation in a clinical trial does not invariably threaten the *most important* interests of the participant. This will depend on the nature and purpose of the trial, including the risks that are faced by the participant.

Many theorists insist that participation in a clinical trial, at least of those who are unable to consent, should only take place where there is 'clinical equipoise', wherein there is a legitimate division of opinion within the scientific community on whether one treatment (typically a proposed experimental treatment) is more efficacious than another (typically the conventional treatment) and the evidence is insufficient to adequately resolve the matter.<sup>81</sup> Even where there is clinical equipoise, the patient could still have an interest in not being entered into a clinical trial. Participation in the trial could be contrary to the patient's previously expressed views and values (e.g. the patient could have expressed strong opposition to clinical trials as such or to something that is an inherent part of the specific clinical trial) and participation will inevitably involve some risk for the participant: '[a]ll clinical research includes non-therapeutic interventions that place the subject at risk with no prospect of direct benefit'.<sup>82</sup> As was highlighted earlier, trial designs that are intended to

<sup>78</sup> It is necessary to distinguish between rights and interests within deontological positions only if we adopt the will conception of claim-rights. The interest conception would classify all relevant interests as claim-rights. Compare: H. L. A. Hart, 'Are There Any Natural Rights?', *The Philosophy Review*, 64 (1955), p. 175, H. L. A. Hart, 'Definition and Theory in Jurisprudence', *Law Quarterly Review*, 70 (1954), p. 37, and N. MacCormick, 'Rights in Legislation' in P. Hacker & J. Raz, eds, *Law, Morality and Society* (Oxford, UK: Clarendon Press, 1977).

<sup>79</sup> I refer to 'waiving the benefit of the right', rather than 'waiving the right', because only the former is compatible with the inalienability of the relevant rights.

<sup>80</sup> Some deontological theorists do hold that all human beings have equal status: see, for example, J. Finnis, 'The Rights and Wrongs of Abortion: A Reply to Judith Thomson', *Philosophy and Public Affairs*, 2 (1973), p. 117, and J. Keown, *Euthanasia, Ethics and Public Policy: An Argument Against Euthanasia* (Cambridge, UK: Cambridge University Press, 2002). But, in contrast, others hold that not all human beings have equal status: see, for example, A. Gewirth, *Reason and Morality* (Chicago, IL: Chicago University Press, 1978), and S. D. Pattinson, *Influencing Traits Before Birth* (Aldershot, Hampshire: Ashgate, 2002).

<sup>81</sup> Compare: B. Freedman, 'Equipoise and the Ethics of Clinical Research', *New Journal of Medicine*, 317 (1987), p. 141 and F. G. Miller and H. Brody, 'What Makes Placebo-Controlled Trials Unethical?', *American Journal of Bioethics*, 2(2) (2002), p. 3.

<sup>82</sup> McRae and Weijer, 'Lessons from Everyday', at p. 1149.

produce generalisable knowledge are therefore not restricted to the therapeutic needs of the specific patient nor can everyone be assumed to accept the need for their participation in emergency research with its attendant non-therapeutic procedures and data collection. Nonetheless, not all deontological theories will hold that any possible interest possessed by the patient will automatically override the interests of all others potentially affected by the trial.

Even where the participant has the ability to consent, a powerful argument can be made to the effect that there may sometimes be a moral duty to participate in some types of research,<sup>83</sup> which is not to say that such a duty should be legally enforced. The conditions for the imposition of moral duties to assist those in need have been fully explored in the literature, from both deontological and utilitarian perspectives.<sup>84</sup> The generally accepted conditions are: (1) the assistance must be required to protect another's important interests; (2) the person on whom the burden of assistance falls must be in a position to assist; (3) the assistance must not impose an unreasonable burden; and (4) the persons requiring assistance must not be in a position to self-assist. A clinical trial that is well designed to test the safety and efficacy of a potentially life-saving therapy will clearly satisfy the first two and last of these conditions, and those imposing only negligible risk on the participant will surely also satisfy the third condition. In such circumstances, it cannot be the case that the interests of the participant are overriding. If this analysis is correct, it surely follows that to hold that a person who is able to consent can never have a moral duty to participate in a clinical trial is effectively to reject all positive duties. That is because if it is accepted that satisfaction of these four conditions gives rise to positive duties, then there must sometimes be a positive duty to participate in some types of medical research.

While the Directive's prevalence principle shares the deontological basis of the formulations of the principle in the Helsinki Declaration, it is expressed in a stricter form than the 2008 version of the Declaration. Requiring that the interests of 'the patient' should 'always prevail' over those of 'science and society' is more demanding than requiring the 'well-being' of the 'research subject' to take 'precedence' over 'all other interests'. *Patients* include those who have not been entered into a clinical trial, whereas *research subjects* do not. The *interests* of the patient are potentially wider than the *well-being* of the individual, and thereby include privacy and non-experiential interests.<sup>85</sup> There is no ambiguity in concluding that an interest that *always prevails* is a conclusive consideration; whereas something could plausibly be said to *take precedence* where it is simply given the first and most serious consideration without being unequivocally overriding. The Directive's prevalence principle is therefore particularly open to the criticism that it unduly elevates the interests of actual and potential participants. The only limit on the prevalence of the participant's interests recognised by the Directive are those contingently accepted by the participant or the participant's legal representative when they provide prior consent. This means that the prevalence principle potentially goes far beyond ensuring that the researcher's professional interests and the pharmaceutical company's commercial interests do not take priority over the most important human rights of each participant.

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<sup>83</sup> See, for example, J. Harris, 'Scientific Research is a Moral Duty', *Journal of Medical Ethics*, 31 (2005), p. 242.

<sup>84</sup> See S. D. Pattinson, 'Consent and Informational Responsibility', *Journal of Medical Ethics*, 35 (2009), p. 176 and further A. Gewirth, *Reason and Morality* (Chicago, IL: Chicago University Press), pp. 217–230; J. Harris, *The Value of Life: an introduction to medical ethics* (London, UK: Routledge & Kegan Paul, 1985) chs 2–3, esp. p. 57; P. Singer, *Practical ethics* (Cambridge, UK: Cambridge University Press, 1993) pp. 229–246; and J. Rawls, *A Theory of Justice* (Oxford, UK: Oxford University Press 1973), p. 114. Compare R. Nozick, *Anarchy, State and Utopia* (Oxford, UK: Blackwell, 1974).

<sup>85</sup> I here use the phrase 'non-experiential interests' to refer to interests in what happens to you even when you are not physically affected by, or conscious of, the relevant conduct.

In the Regulation proposed by the European Commission, the prevalence principle has been re-worded to become: ‘The rights, safety and well-being of the subjects shall prevail over the interests of science and society’.<sup>86</sup> This move from ‘the interests of the patient’ to the ‘rights, safety and well-being of the subjects’ is to be commended as a move away from a presumption against research. The reformation of the principle continues to treat the (now specified) interests of participants as automatically overriding the ‘interests of science and society’, which on the face of it remains problematic even within a deontological perspective. There are, however, two important counter points. First, the principle is to be regarded as subject to the other provisions of the draft Regulation, because the Regulation would otherwise be contradictory. In particular, the prevalence of the participants’ rights, safety and well-being must be regarded as consistent with the conduct of emergency research in accordance with the terms of the Regulation. Secondly, there is an alternative justification for requiring the participant’s interests to be treated as if they were prevalent *even if they do not strictly have this weight*. This alternative justification rests on the precautionary principle that it is better to over protect the rights of participants than to under protect them. This principle would support treating the rights of participants as if they were prevalent to remove the opportunity for abuse created by attempts to specify circumstances in which their rights may be overridden. Thus, the draft Regulation’s prevalence principle can be defended. This is important, because the prevalence principle has wider implications than is commonly recognised.

### **Ensuring a proper balance of the interests of participants and other interests in the absence of prior consent**

The draft EU Regulation proposes to remove the safeguard of informed consent to permit emergency research. One benefit of the prior consent requirement, however, is that it enables account to be taken of the participant’s views, values, and preferences and thereby serves to reduce the likelihood that the participant’s interests will be overlooked. Thus, extra care needs to be taken to ensure that whatever rights/interests participants have are properly overridden by competing rights/interests, the benefits of the research are maximised, and that factors that artificially magnify or protect the interests of persons other than the participant are minimised. The many factors that are likely to distort the balance between the interests of the participant and the interests of others are, therefore, of particular importance in the context of emergency research.

One factor that needs to be addressed in this context is the ‘sponsorship bias’. This refers to pharmaceutical funding being associated with the production and publication of pro-industry results in clinical trials.<sup>87</sup> The bias produced by commercial conflicts of interest has been reported to influence the design of trials (such as by the choice of comparators, dosages, protocols, or trial durations)<sup>88</sup> and their reporting (such as the selection of which trials to

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<sup>86</sup> Article 28(2)(d).

<sup>87</sup> See, for example, H.T. Stelfox, and others, ‘Conflicts of Interest in the Debate Over Calcium-Channel Antagonists’, *New England Journal of Medicine*, 2 (1998), p. 101; J.E. Bekelman, and others, ‘Scope and Impact of Financial Conflicts of Interest in Biomedical Research’, *Journal of the American Medical Association*, 289 (2003), p. 454; J. Lexchin, et al. ‘Pharmaceutical Industry Sponsorship and Research Outcome and Quality: Systematic Review’, *British Medical Journal*, 326 (2003), p. 1167; M. Bhandari, et al. ‘Association between Industry Funding and Statistically Significant Pro-industry Findings in Medical and Surgical Randomized Trials’, *Canadian Medical Association Journal*, 170 (2004), p. 477.

<sup>88</sup> V. M. Montori et al. ‘Users’ Guide to Detecting Misleading Claims in Clinical Research Reports’, *British Medical Journal*, 329 (2004), p. 1093.

submit for publication and, when a trial is selected, use of a ghost-writer whose authorship is not declared or a guest author who has not conducted the research).<sup>89</sup> According to Angell,

companies are involved in every detail of the research—from the design of the study through analysis of the data to the decision whether to publish the results. That involvement has made bias not only possible but extremely likely.<sup>90</sup>

Many potential remedies for sponsorship bias have been suggested in the literature, some of which would need to operate at a regulatory level. One of the most widely recommended is the establishment of a public registry of all clinical trials,<sup>91</sup> which the European Union has recently sought to implement.

The EU Clinical Trials Register was launched by the European Medicines Agency in March 2011.<sup>92</sup> This online register grants public access to information on clinical trials of medicinal products authorised under the Clinical Trials Directive. At the time of writing, this register contains the details of over 18,000 clinical trials, derived from the EudraAct database established by Article 11 of the Clinical Trials Directive. This registry should remove some of the distortion created by the non-publication of unfavourable trial results and enable detailed independent analysis of all registered trials. A register cannot, however, address all aspects and consequences of the sponsorship bias. It cannot, for example, directly affect the design of trials or prevent sponsors from arranging for articles to be submitted to journals reporting their clinical trials in the most favourable light, using ghost-writers and guest authors. A register does enable retrospective analysis of the effects of the sponsorship bias, but it does not address the distorting effect of the sponsor's control over the details of the research.

Lewis and others have argued that 'as long as drug companies retain primary responsibility for conducting or funding clinical trials, the trials will be sub-optimal from the standpoint of public health and safety'.<sup>93</sup> They opine that the only way to eliminate sponsorship bias is by the adoption of a radical solution: removing the direct link between the clinical trial sponsor and the drug tester. They advance the view that clinical trials should not be directly funded or controlled by pharmaceutical companies; instead an independent public agency should be established to conduct the trials. They further propose, focussing their analysis on the US, that this body be funded by a tax on pharmaceutical companies.

This is a radical proposal. It would need to be properly trialled first and emergency research presents an ideal opportunity for such trialling in the UK, because (unlike many types of elective treatment) emergency treatment takes places within the National Health Service (NHS). In theory, such a system could be overseen by the recently established body that is intended to provide a one-stop-shop for research applications in the UK: the Health Research Authority.<sup>94</sup> There are, however, many obstacles to central control over the conduct of clinical trials. For a start, it would require the support of the leading journals, because

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<sup>89</sup> On which see B. Moffatt and C. Elliott, 'Ghost Marketing: Pharmaceutical Companies and Ghostwritten Journal Articles', *Perspectives in Biology and Medicine*, 50 (2007), p. 18.

<sup>90</sup> M. Angell, *The Truth About Drug Companies: How They Deceive Us and What to Do about it* (New York, NY: Random House, 2004), p. 100.

<sup>91</sup> Suggested by, for example, Bekelman et al., 'Scope and Impact', p. 464, Lexchin et al., 'Pharmaceutical Industry', p. 9 and Montori et al. 'Detecting Misleading Claims', p. 1096.

<sup>92</sup> <https://www.clinicaltrialsregister.eu/> (accessed 23 June 2012).

<sup>93</sup> T.R. Lewis, J.H. Reichman and A.D. So, 'The Case for Public Funding and Public Oversight of Clinical Trials' *Economist's Voice*, 4.1 (January 2007). [http://works.bepress.com/tracy\\_lewis/2](http://works.bepress.com/tracy_lewis/2) (accessed 22 June 2012).

<sup>94</sup> Available at: <http://www.hra.nhs.uk> (accessed 22 June 2012). The HRA was established as a Special Health Authority by the Health Research Authority Directions, passed under the NHS Act 2006, in December 2011.

otherwise pharmaceutical companies would simply submit for publication the results of trials conducted outside of this body's control, perhaps even conducted outside of the EU. The biggest obstacle is that such a system would require concerted political support in the face of what may be anticipated as powerful lobbying from the pharmaceutical industry. There are no indications that such support exists in the UK, let alone the EU as a whole.

The reality is that the Clinical Trials Directive was 'industry-led' in the sense that its principal purpose was to make conducting clinical trials in Europe more attractive to researchers and their sponsors.<sup>95</sup> There is already a view that the Directive has unduly hindered research. The 2011 report of the Academy of Medical Sciences (AMS) declared that the Directive has actually 'increased the administrative burden and cost of clinical trials for both non-commercial and commercial sponsors with no discernible improvements to patient safety or to the ethical basis of clinical trials'.<sup>96</sup> Further, the AMS opines, the UK has aggravated this problem because the Clinical Trials Regulations so closely reflect the wording of the Directive as to amount to a 'more robust and rigorous interpretation'.<sup>97</sup> It was shown above that that this view is not borne out by the UK's response to emergency trials. It is therefore perhaps not surprising that the 125 page AMS report barely mentions emergency research, save for citing as an example of delay the significant time that it took for NHS approval to be obtained for a recent multicentre trial comparing two types of emergency intervention for ruptured aortic aneurysm.<sup>98</sup> In response to the AMS report, the UK government has indicated that it will seek 'to further reduce burdens on industry' in EU Level negotiations.<sup>99</sup> It is therefore unlikely that the UK would support a radical solution to the problem of sponsorship bias. This is unfortunate because the distorting effect of this bias can only be eliminated by a radical rethinking of the relationship between the interests of pharmaceutical companies and the interests of participants, future patients, and science.

## Conclusion

This article has argued for reform of the EU legislation addressing emergency research on medicinal products and supported the relevant provisions of the Regulation proposed by the European Commission in July 2012. It has, in particular, defended an exception to the prior consent requirement, removal of the conditions that favour conducting emergency research on children over incapacitated adults, and a reformulation of the principle stating the terms of the relationship between the interests of the participants and the interests of science and society. The replacement of the Clinical Trials Directive will not, however, fully address the distortions that potentially undermine the proper balance between the interests of participants and others. The prevalence principle, and the precautionary principle argued to underpin it in 'The rights and interests of the participant' section, require that we at least trial more radical policies specifically directed at the distorting influence of the commercial interests of pharmaceutical companies. Such policies are particularly important in the context of emergency research given the prospective removal of the safeguard of informed consent.

## Funding

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<sup>95</sup> See E. Cave and S. Holm, 'New Governance Arrangements for Research Ethics Committees: Is Facilitating Research Achieved at the Cost of Participants' Interest', *Journal of Medical Ethics*, 28 (2002), p. 318.

<sup>96</sup> AMS, 'A New Pathway for the Regulation and Governance of Health Research' (January 2011), p. 43.

<sup>97</sup> AMS, 'Health Research', p. 52.

<sup>98</sup> AMS, 'Health Research', p. 35 (the IMPROVE trial).

<sup>99</sup> HM Treasury and Department for Business and Innovation Skills, *Plan for Growth* (London, UK, March 2011), para. 2.196.

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