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Fossil relics: ethics committees under the European Clinical Trials Regulation

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Abstract

The stated purpose of the European Clinical Trials Regulation is to facilitate recruitment to multi-national clinical trials across Europe by requiring all applications for authorisation to be submitted through a central portal from which a joint assessment of the scientific merits of the research will be conducted between the participating member states. Beyond that, the Regulation leaves it to each member state to decide how it will organise the authorisation of that research within its own country. This gives great flexibility in how each member state shall order the role of the national ethics committee. There are two questions to answer that will determine the future of ethics committees in Europe. First, should the ethics committee be permitted to contest the scientific validity and safety of the research protocol? Secondly, if they must engage with the science, then what is the best way to organise the ethics committee in their collaboration with other regulatory bodies involved in the authorisation of that research? The effect of the Regulation is to put ethics committees in Europe at a vital cross-roads that could see them restricted to what would be, for the most part, a consideration of the legality of the protocol. But new regulatory bodies could be established under the Regulation that might adopt 'integrated regulation' and thereby better serve the human subject in research.

Introduction

The 2001 Clinical Trials Directive prescribed common standards and structures for the regulation of clinical drug trials in Europe. At its core was a formal process of authorisation by a national competent authority and an ethics committee in which each made a separate decision within their own regulatory domain. Its critics have pointed to delays, unwieldy bureaucracy that has purportedly hit academic researchers the hardest, and the resulting problem of how to co-ordinate a multi-national clinical trial across Europe. The Directive will therefore be replaced by the European Clinical Trials Regulation (EU) No. 536/2014. It will be implemented in the near future. An inclusive debate on what the Regulation means for ethics committees in Europe is already

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lacking and overdue. The author questions whether the research ethics community appreciates the significance of this new legislation. It presents a potentially severe threat to the correct role of the ethics committee but also an unrivalled opportunity for the radical re-ordering of the regulatory apparatus for clinical trials. The potential of the Regulation lies not in what is explicit, but rather in what the Regulation leaves unstated. The root of the matter is the way that the Regulation provides for the review of the science and the ethics of a research protocol.

Fault lines in the Directive: the science and ethics split

At the core of the Directive is the requirement to weigh the societal value of the proposed research against its risks and benefits to the research subject and to justify the result.[1] The Directive requires that this assessment be conducted by the ethics committee and/or the 'competent authority' in the member state. So it allows for variation between member states as to which of these entities shall make the initial assessment of the science and safety of the protocol upon which the final decision on risk and benefit must be based. The competent authority is responsible under the Directive for carrying out inspections of research facilities but in practice it could be the same body responsible for the safety of drugs licensed to market. So there is justification for requiring the competent authority to give an assurance on the safety of the drug under test. However, the Directive places a separate legal duty upon the ethics committee to make the final decision as to whether this initial assessment of risk and benefit is 'satisfactory and justified'.[2] This compounds a problem at the root of the Directive, namely that the discharge of these legal duties concerning the assessment of risk and benefit requires the competent authority and the ethics committee *to communicate with each other*. The author has demonstrated that this requirement of communication has been neglected in the United Kingdom.[3] It has been stated elsewhere *that most member states show no interaction at all between ethics committee and competent authority in the authorisation of a clinical trial.*[4]

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1 2001/20/EC Article 3(2)(a).

2 2001/20/EC Article 6(3)(b).

3 C.L. Roy-Toole, 'TGN1412 Remembered: the scientific duty of the ethics committee', *Journal of Medical Law and Ethics* 4:1 (2016), 39-54.

4 Piret Veerus, Joel Lexchin & Elina Hemminki, 'Legislative regulation and ethical governance of medical research in different European Union countries', *Journal of Medical Ethics*; 0; 1-5, published on 10 May 2013 as doi:10.1136/medethics-2012-101282, retrieved on 15 September 2015.

For Kenter and Cohen, writing before the passage of the Regulation into European law, there was no value in replacing the Clinical Trials Directive without first addressing what they saw as the fundamental weakness in the regulatory apparatus of clinical research in Europe: the two-tier system in which the ethics committee and national competent authority both evaluate the same research application, but on the erroneous assumption that scientific assessment can be separated from ethical review.[5] The author concurs that, within the process of ethical review, an assessment of the scientific validity and safety of the design cannot be divorced from the wider ethical consideration of the risks and benefits to the human subject in research and to the patient population as a whole.[6] Our statements conform to those issued by CIOMS in its 2002 Guidance which asserted that scientific review and ethical review cannot be separated.[7]

Do as thou wilt: flexible approaches to research governance under the Regulation

This is the shape of things to come under the European Clinical Trials Regulation (CTR). In line with the Directive, the CTR requires that there must be an ethics committee that is an independent body in a member state. An ethics committee must conduct an ethical review for every clinical trial. There must be a competent authority, but it is responsible for inspections and nothing else.[8] In this, the CTR has an odd quality to it. European Directives are permissive up to a point, in that they set out over-arching legislative aims which EU member states are expected to transpose to domestic law in accordance with the principle of subsidiarity. European Regulations, by contrast, are prescriptive in that these impose legal requirements on each member state directly according to a single legislative template. But, unlike the Directive, the CTR is in no way prescriptive as to what an ethics committee is meant to do or what the ethical review must contain.[9] Nor does it prescribe for the continuation of the two-tier system that sprang up under the Directive for

5 M.J.H. Kenter & A.F. Cohen, 'Re-engineering the European Clinical Trials Directive', *Lancet* 379 (12 May 2012), 1765.
6 C.L. Roy-Toole, 'TGN1412 Remembered: the scientific duty of the ethics committee', *Journal of Medical Law and Ethics* 4:1 (2016), 39-54.
7 Council for International Organisations of Medical Sciences (CIOMS) in collaboration with the World Health Organisation (WHO), International Ethical Guidelines for Biomedical Research involving Human Subjects, 2002, Commentary on Guideline 2, at p. 24.
8 Regulation (EU) No. 536/2014 Article 2(2)(11), Article 2(2)(31).
9 *Ibid*. Article 4.

the assessment of clinical trial protocols by an ethics committee and a national competent authority. This looseness of drafting is deliberate.[10]

The intention of the European Parliament is to produce a flexible legal framework that enables each member state to make its own arrangements for the inter-action between the ethics committee and the 'appropriate body or bodies' involved in the authorisation of a clinical trial.[11] In the author's estimation, the most important feature of the CTR is that *it allows for new entities to be created to assess the science of the protocol and the safety aspects of the research and to engage with an ethics committee to produce a 'single administrative decision'* on the authorisation of a clinical trial.[12] This could do away with the current paradigm of separate assessment of science, safety and ethics by a competent authority and an ethics committee.

'National Ethics': a twin-track approach to multi-national clinical trials

The primary aim of the CTR is to put into law that which was hitherto only a rule of administrative practice: the Voluntary Harmonisation Procedure for multi-national clinical drug trials (VHP).[13] VHP was intended to enable national competent authorities to arrive at a speedy consensus on the scientific validity and safety of a multi-national clinical drug trial, thereby enabling the national ethics committees to concentrate on matters that were seen as having application within the national boundaries of their own states. The CTR now puts a legal framework in place for this. But it is a framework based on a doubtful premise.

The CTR assumes that the assessment of the risks and benefits of the research can be conducted through a scientific and technical collaboration between agencies at a multi-national level. But the CTR states that certain matters relating to the authorisation process are to be dealt with on a solely national basis by the institutions concerned.[14] This is because the CTR treats as 'national' various matters that are more correctly classified as being wholly legal in character or else determinable in part by reference to national laws.[15] Other matters of a solely national scope concern assessments of the suitability of the local research

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10 *Ibid.* Recital 7.
11 *Ibid.* Recital 18.
12 *Ibid.* Recital 17.
13 Heads of Medicines Agencies Clinical Trials Facilitation Groups: Guidance document for sponsors for a Voluntary Harmonisation Procedure (VHP) for the assessment of multinational Clinical Trial Applications, Version 3.1, June 2013.
14 Regulation (EU) No. 536/2014 Recital 6.
15 *Ibid.* Article 7(1)(a), (b), (c), (d), (g) and (h).

site and the researcher.[16] Of itself this two-fold classification is not objectionable. But it becomes objectionable if a tendency arises to treat ethics as having a purely territorial domain. It makes it easier to separate the scientific and technical assessment of the risks and benefits of a multi-national clinical trial from its ethical underpinning and so too from the domain of the ethics committee. Ultimately, it is a moral judgment as to what constitutes an acceptable risk to the research subject. It is not a quantitative assessment of a purely technical character. There were Nazi doctors and other researchers involved in the exploitation of vulnerable patients who no doubt considered their actions to be justified by reference to their idea of the greater good. This demonstrates that scientific review and ethical review occupy overlapping domains which cannot be separated intellectually, despite the practices that have emerged in the course of the implementation of the Directive. The CTR therefore requires every clinical trial to be subjected to '*scientific and ethical review*' before authorisation can be made.[17] But the phrase displays a studied ambiguity. The Proposal for a Regulation included a perfunctory statement that science and ethics cannot be split.[18] Had that statement been better worded to state that it is the review of the science and the ethics of a protocol which cannot be separated, then it would have affirmed the CIOMS 2002 Guidance which requires the ethics committee to deal with the science of the protocol. As it is, this statement is absent from the final text of the CTR.

The compartmentalisation of ethics: Part I and Part II assessment

The CTR legislates for the conduct of ethical review and it does so in a striking manner. The CTR takes the 'holistic' notion of ethical review as defined under the CIOMS 2002 Guidance and breaks it up, rather arbitrarily, into separate components that can be allocated to various bodies to perform according to the legislative will of the member state. This compartmentalisation of ethics under the CTR is known as 'Part I and Part II of the assessment report for the authorisation of a clinical trial'.[19] Part I contains the assessment of the risk and benefit of the research to the trial subject and to the wider public and which is to be carried out with regard to the scientific validity of the design and the safety of the drug. Part II contains aspects that are to be assessed only with regard to their application within the territory covered by the assessing body.

16 *Ibid*. Article 7(1)(e) and (f).
17 *Ibid*. Article 4.
18 European Commission: Proposal for a Regulation, COM(2012) 369 Final, in the Explanatory Memorandum at Section 3.2.
19 *Ibid*. Articles 4, 6 and 7.

These include consent, subject recruitment in line with the requirements of Chapter V of the CTR, data protection, compensation and insurance. The Part II aspects require the protocol to be assessed for compliance with legal standards set out in the CTR. All of these components must be addressed in the final assessment report that a member state must conclude in order for a clinical trial to be authorised.

The CTR allows each member state to decide if their ethics committees shall play *any* role in the Part I or Part II assessment. A member state might decide to grant the ethics committee the power to make a final review of all aspects of the Part I and Part II assessment that an 'appropriate body' has separately carried out. That would give the ethics committee the power to conduct a full ethical review within the meaning of the CIOMS 2002 Guidance and it would also amount to a secondary review of the science. *Or the member state might decide to confine the role of the ethics committee only to a discrete part of the assessment process.* If the role of the ethics committee were to be circumscribed in this way, then an 'appropriate body or bodies' would have to be nominated to conduct those aspects of the Part I and Part II assessment that the ethics committee could not. In this way, the CTR allows the role of the ethics committee to be curtailed radically by legislative action.

The Directive specified that the final decision on risk and benefit had to lie with the ethics committee. The CTR does not do this. Rather, the CTR permits the separation of scientific review from the domain of the ethics committee. *It enables the vital function of risk and benefit assessment to be carried out by a body that is not an ethics committee*. Thus, a problematic feature of the Part II assessment is that a decision on the recruitment of special groups such as incapacitated adults, minors, pregnant women and emergency cases requires a consideration of the therapeutic risk and benefit to the trial subject as a threshold for admittance to the trial. Since the assessment of risk and benefit is to be found in the Part I assessment, it raises an awkward possibility that an ethics committee will be required to make a decision on the recruitment of national citizens to a clinical trial and be bound in this by a scientific assessment that has been carried out by some 'appropriate body' other than the national ethics committee, perhaps one located in another country. If ethics committees are restricted in their consideration to those matters contained in the Part II assessment only, then they *could* be shut out from comment on matters relating to the scientific and technical aspects of the research, *and also matters relating to clinical practice and subject care in the research*. This strikes at the integrity of ethical review in the sense contemplated by CIOMS in its 2002 Guidance. Comments made by Lord Warner to the Chief Executive of the United Kingdom's Health Research Authority in a Parliamentary Select Committee evidence session in 2013 suggest that he might welcome a legislative opportunity to prevent research ethics committees from re-examining the science of a protocol.[20] The author anticipates

that this will be the next major threat to the competence of research ethics committees in the United Kingdom. A similar threat could be posed to ethics committees in Europe.

Sweeping up after the competent authority: a residual role for ethics committees

If ethics committees are shut out from the Part I assessment, and have no oversight of the matter of risk and benefit assessment, then the main role left open to them would be to examine the legality of the protocol. The assessment of site suitability and researcher competence could be farmed out to other agencies to perform. There would be no need to retain ethics committees in any way separate to the appropriate body that deals with the authorisation of the clinical trial. The job of the Part II assessment could then be done more usefully by a team of lawyers and insurance experts operating within a single regulator for clinical trials. That proposition might meet with the objection that the CTR mandates the existence of an ethics committee. But since ethics under the Part II assessment is chiefly an application of the law to the protocol, there is no great substance to that objection. A network of semi-redundant ethics committees would simply not be justified in public cost and administrative delay. Only their managers would benefit.

Puzzlingly, the CTR confers upon the ethics committee a power to veto a clinical trial by issuing a 'negative opinion in accordance with the law of the member state concerned that is valid for that entire member state'.[21] But this is not to guarantee the ethics committee the last word on the risks and benefits of a clinical trial, as was seen under the Directive. The CTR leaves it to national legislatures to decide the basis on which that negative opinion is to be issued. It is impossible to see how national laws could exclude the ethics committee from playing a part in the Part I assessment process, and yet allow the ethics committee an unrestricted power of veto, unless the ethics committee were to retain the power to make a secondary review of the science and of any prior assessment of the risks and benefits of the protocol. The author anticipates political pressure to restrict the national ethics committee's veto so that it might only be exercised with regard to the matters in the Part II assessment, these being mainly matters relating to the legality of the protocol.

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20 Parliamentary Joint Committee on the Draft Care and Support Bill: Draft Care and Support Bill, Session 2012-2013, Oral Evidence at Q.299.

21 Regulation (EU) No. 536/2014 Article 8(4).

Integrated Regulation: the way forward for clinical trials

The author posits that ethics committees in Europe, and in the United Kingdom especially, have been rendered dysfunctional by years of policy neglect and by their practical separation from the national competent authorities. The way to cure that is to take advantage of what the CTR offers and to devise *integrated regulation* for clinical trials by which the ethics committee is embedded within the national competent authority *and collaborates with it in the Part I assessment*. This new body becomes a true single regulator for clinical trials and is an 'appropriate body' for this purpose. This functional integration should enable the ethics committee to receive scientific support in real time to assist in its ethical review. That in turn *should* enable it to provide an ethical and legal safeguard to what the competent authority does in the management of the scientific and technical aspects of the research. The effectiveness of the ethics committee as a custodian of regulatory morals will depend very much upon protecting its quality of independence. The ethics committee can only be truly independent if it has the skill to challenge other actors in the regulatory process. It must also have the will to challenge. This can only be accomplished by the recruitment of skilled experts and these can only be incentivised by payment. *Their paymaster must be independent of the national competent authority, or the body that replaces it.*

There is a counter-argument to this. Kenter and Cohen remarked that only a small proportion of clinical research involves drug trials and that there are numerous other types of research that bring just as much risk as a clinical trial. This observation is of critical importance to the debate. They assert that expanding the role or resources of the 'drugs regulatory authorities' (meaning the licensing authorities and/or competent authorities) would not achieve the goal of integrated ethical and scientific review because these bodies have no legal power to deal with research other than clinical drug trials. They also remark that it would be impossible as a matter of resource, and prohibitive as a matter of cost, to provide the full spectrum of scientific expertise required for the review of all research projects and to put this all under one roof in one centralised body. The *New Pathway* report made a similar observation in setting its face against an enlarged Medicines and Healthcare products Regulatory Agency (MHRA) in the United Kingdom.[22]

Instead, Kenter and Cohen wish to see ethics committees undertaking scientific review with the help of a pool of academic experts drawn from the brightest and the best. This pool of expertise would be administered by 'health

[22] The Academy of Medical Sciences: A new pathway for the regulation and governance of health research, January 2011, section 9.3.

research authorities' in each EU member state. Eventually, these experts could be made available on a trans-national basis to facilitate the provision of a single opinion on a clinical trial protocol that is valid across the EU Area. At the time of their writing, Kenter and Cohen took inspiration from the UK Government's proposal for the UK Health Research Authority, which had been established in December 2011. But as a practical model for a real health research authority, they suggest the Dutch *Centrale Commissie Mensgebonden Onderzoek* (CCMO). For the author, the debate turns on the relative merits of *integrated regulation* by merger and re-organisation as against Kenter and Cohen's proposal for '*integrated assessment*' by omni-competent ethics committees.

Clinical drugs trials in the Netherlands require 'dual review' by an ethics committee and the competent authority. These function as separate entities. There are local ethics committees and the CCMO is the central ethics committee. The CCMO is also a specialised ethics committee on advanced therapies and similar applications, and a standards body for persons who serve on the local committees. The CCMO can also function as the national competent authority for clinical drug trials. But when it acts as an ethics committee for clinical trials, the CCMO will call upon the Ministry of Health, Welfare and Sport to act as the competent authority. The competent authority will perform a 'marginal review' to check for 'motivated objections' against the study, including adverse reactions. So whilst the CCMO has 'amphibian' characteristics, in that it is capable of assuming the role of ethics committee *or* competent authority, it is not an integrated regulator which provides the function of ethics committee *and* competent authority.

The author questions why the CCMO should be taken as a model for universal application across Europe and suggests that its merits are peculiar to its own country. Gordijn remarked that ethics committees have been comparatively easy to establish in the Netherlands because of its 'natural affinity to deliberative structures and consultative bodies'.[23] And this is the fatal objection to the recommendation that Kenter and Cohen put forward. They see the world as educated Dutchmen. They presume that *all* European governments might show the political will to spend money on ethics committees in order to improve quality in research governance. The author views the world as an Anglo-Saxon. He surmises that the research governance policy for the United Kingdom these last ten years has been predicated on the unspoken notion that ethics committees are a burden and a bore and that the best way to get ahead in the market for research is to get around them. He concedes that Kenter and Cohen advance the ideal in the form of sage ethics committees backed by a national health research authority with a comprehensive pool of expertise at its disposal. But it

23 See further B. Gordijn, 'Ethics Committees in the Netherlands', in J. Glasa (ed.), *Ethics Committees in Central and Eastern Europe* (Strasbourg: Council of Europe, 2000).

will never happen because there is no political or financial incentive to make it happen, at least not in the United Kingdom. The questionable progress of the UK Health Research Authority demonstrates this very clearly.

Quantity before Quality: the case of the UK Health Research Authority

The UK Health Research Authority (HRA) is a very different entity to the Dutch CCMO. The HRA has no statutory function as the competent authority and not enough expertise available within it to become one. The HRA is moving in a quite different direction to that envisaged by Kenter and Cohen. Its chief focus of effort and expense is to accelerate and to increase the volume of research approvals in the pipeline by centralising as many approvals as it can that are needed for this research to commence. This it hopes to do through its fledgling Assessment and Approval scheme. This aims to take management responsibility for research approvals away from the National Health Service, where it legally and rationally belongs, and to vest it in the HRA, which is expanding its own managerial base to fit its own plans. The HRA then aims to give an assurance that research is ethically sound and legally compliant, and the NHS is expected to rely upon this assurance where research takes place on its sites. The only incentive for the National Health Service to accept this scheme is the expectation that the HRA and the ethics committees *should assume a legal liability to indemnify and to compensate the NHS for all losses arising from their error in this approval process.*[24]

The HRA does not even regard Kenter and Cohen's notion of integrated assessment as a desirable policy aim. UK ethics committees are instructed that it is not their role to review the science. What is worse, the HRA appears to be failing conspicuously to deliver any sort of independent scientific review to all but a small fraction of ethics committees.[25] There are no Scientific Officers to support the ethics committees and the HRA has not provided a pool of independent experts who are accredited and available to assist the research ethics committees with the science.[26] It follows that ethics committees are not equipped to give the ethical assurance required of them under the scheme. When measured against the original criteria set by Kenter and Cohen for a health research

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24 United Kingdom Health Research Authority: UK policy framework for health and social care research, issued for comment, version 1.0, February 2015 at section 8.18.

25 C.L. Roy-Toole, 'TGN1412 Remembered: the scientific duty of the ethics committee', *Journal of Medical Law and Ethics* 4:1 (2016), 39-54.

26 J. Wisely & J. Lilleyman, 'Implementing the district hospital recommendations for the National Health Service National Research Ethics Service in England', *Journal of Medical Ethics* 33 (2007), 168.

authority, it appears that the UK HRA has already 'gone off the rails'. Yet it does show the likely direction of travel for similar health research authorities that might be established in other member states. Top-heavy management fixated on cost cutting and volume output, all at the expense of decisional quality, is the end stop on this line.

TGN1412: the duty to avoid another

The TGN1412 study resulted in one the worst clinical accidents in living memory. This first-in-class monoclonal super-agonist was trialled on young healthy volunteers and severe injuries resulted to six of them in the ensuing 'cytokine storm'. The trial was approved by an ethics committee in the United Kingdom which was not required by the terms of their guidance to examine the science for themselves and yet had no report from an immunologist independent of the sponsor and dealing with the design of the study. The ethics committee did not challenge the standard practice of the industry, nor indeed of the regulators, to allow a short interval dosing regimen whereby the six injured volunteers were denied the precaution of an adequate observation interval. Had the ethics committee been encouraged to contest the science of the protocol, and had it been supplied with a more diverse pool of independent expertise, then it might have challenged the design, and the risk to benefit assessment, in a way that the competent authority failed to do.[27] TGN1412 is a warning against the separation of scientific and ethical review and against the two-tier system in Europe whereby ethics committee and competent authority fail to communicate or collaborate. The risk of another major accident is not confined to Phase I trials of new drugs. Phase II studies involving licenced drugs in novel combinations or dosages might also pose unknown risks of comparable magnitude.

Something has to be done to reduce avoidable harms and if this can only be done for clinical trials then that is better than nothing. The author posits that *integrated regulation* for clinical trials is the more pragmatic way to guard against another disaster in the future. The author challenges national regulators to show why it is an insuperable obstacle, or an undesirable aim, to establish ethics committees within a competent authority in a member state. The Belgian Federal Agency for Medicines and Health Products (FAHMP) is already on record as stating that scientific and ethical reviews must be run simultaneously and that the ethics committee and competent authority should reorganise themselves to work 'hand in hand'. FAHMP stated that it wishes to see the in-

27 C.L. Roy-Toole, 'TGN1412 Remembered: the scientific duty of the ethics committee', *Journal of Medical Law and Ethics* 4:1 (2016), 39-54.

volvement of ethics committees in the Part I assessment.[28] Furthermore, the member state that seizes this opportunity presented by the CTR may obtain a national advantage over others that do not, by implementing integrated regulation as a safer yet more efficient model before the rest.

The wider picture: good governance for the clinical research sector

But what of the other types of clinical research? Surgical trials are a peculiar case in point. The author envisages that ethics committees dealing with non-clinical trial research may in future need to move towards *decentralisation*. They may need to become affiliated to the institutions that conduct the research. *They might even become privatised*. That might appear to be a move backwards, especially in view of possible moves towards centralisation of Institutional Review Boards in the United States. But Kenter and Cohen set their face against centralisation because they contended that it was too expensive and could never be resourced properly, although no figures were put forward in support of that proposition. The UK HRA is a highly centralised institution, one that is intent on taking on as many functions as it can in order to secure its own future. It should be anticipated that the HRA will fail for this reason and so it must already be cut down to size.

Even if the UK HRA were to be dissolved tomorrow, there is a subsisting need for an audit body that maintains standards in the organisations which conduct or oversee research. There is a Care Quality Commission for clinical practice in the United Kingdom so there is a need for a comparable body to audit research organisations and ethics committees, especially if they are decentralised, privatised or institutionally affiliated. The point is that the body that carries out the audit should not also be given the monopoly on setting its own rules, as appears to be happening now in the HRA. Monopoly providers become self-focussed and disinclined towards useful dialogue with lesser stakeholders.

There is a need for an independent pool of experts as Kenter and Cohen remarked, but the author questions why this pool could not be maintained by the competent authority, and subsidised by levy on Industry and Academia. It could then be made available to ethics committees that need assistance on protocols involving all forms of clinical research, and it could function as an advice service to those that apply to conduct research. There could be a fee

[28] Dr. Greet Musch, EuropaBio Conference on The Future of Clinical Trials (Brussels, 28 January 2013).

structure put in place so that the use of the pool provides an income stream for the entity that manages it and to defray the cost of its maintenance.

How to make the United Kingdom a model for Europe

In the United Kingdom, the Clinical Trials Unit of the Medicines and Healthcare products Regulatory Agency (MHRA CTU) should take the initiative and strive for efficient regulation by its own efforts. It should adopt integrated regulation for the United Kingdom. The MHRA CTU has an advantage over its comparators already. The Care Act 2014 now enables any group of persons to be recognised by the HRA as an ethics committee, provided that the group can demonstrate a demand for its services.[29] But the Act does not state that the ethics committee needs to be under the management of the HRA or even rooted within the existing research ethics committee system. This provision may well have been drafted with an eye to the formation of independent Phase I ethics committees. But there is no reason why the MHRA CTU should not seek to use the Act to establish its own ethics committees within its own structure and management. A legal challenge would lie against the HRA if it refused to recognise an MHRA CTU ethics committee without sound reason. The combination of ethics committees with MHRA CTU would then enable the United Kingdom to provide a 'single decision' as required by the CTR.

At present, the United Kingdom permits applications for clinical trials authorisation to be submitted to the MHRA or to the current EudraCT central portal operated by the European Medicines Agency. That will change with the implementation of the CTR. The CTR will require all applications for clinical drug trials to be routed through a central submissions portal at European level for the registration of trials and the processing of those applications. These applications will then be routed to appropriate bodies in EU member states so that they might conduct the Part I assessment where required to do so. The challenge for EU member states is to produce national e-management systems for clinical trials that complement the use of the EU portal to produce the single decision. So the author suggests that the e-submission requirements of the CTR would be much better served if the single decision were provided by a combined research ethics committee and MHRA CTU operating under its own proprietary electronic platform for submissions and with direct access to the EU portal. Integration would be needed with regulators for tissues and embryos. But this should not be objectionable because the MHRA has already been acknowledged as the main point for technical advice on advanced therapies. It

29 Care Act 2014, section 114.

would marginalise the HRA in the regulatory system for clinical trials in the United Kingdom because the power to deliver assurances on safety and ethics would then lie with the MHRA CTU, where it more rationally belongs.

Conclusions

Shrinking research budgets and squeezed national health systems in the European Research Area make for disturbance in markets for clinical research that can only be addressed by *efficient* measures in the regulation of research and in the organisation of researchers. Efficiency and competitiveness are not the same. 'Competitive' does not necessarily mean 'safe'. Understanding and achieving a successful interplay between the ethics committee and the competent authority is the key to success under the Regulation. Lobbyists drawn from the pharmaceutical industry and from academic research will be very active with their own agenda over the next few years. So ethics committees need to reflect profoundly upon what they are doing now and upon what they expect to be doing five years from now, unless they are content to become a vestigial remnant in the back row of research governance. The competent authorities must do likewise before their own organisational futures are taken out of their hands by the governments of their own countries. Responsibly minded citizens need to organise and to press for political and legislative action at member state level to achieve what is right for the protection of human subjects in the new operational environment created by the European Clinical Trials Regulation. This is necessary if we are to be serious about avoiding another event like the TGN1412 disaster.

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