MEDICAL RESEARCH INVOLVING INCAPACITATED ADULTS: IMPLICATIONS OF THE EU CLINICAL TRIALS DIRECTIVE 2001/20/EC

KATHLEEN LIDDELL, JULIAN BION, DOUGLAS CHAMBERLAIN, CHRISTIANE DRUML, ERWIN KOMPANJE, FRANCOIS LEMAIRE, DAVID MENON, BOZIDAR VRHOVAC AND CHRISTIAN J. WIEDERMANN*

I. INTRODUCTION

A. The Regulation of Medical Research

Recent legislative developments in Europe, especially in relation to tissue, data and clinical trials, have deeply worried clinical investigators and their academic sponsors. They argue that the array of new laws


(described by one as ‘an ever-growing threnody’)\(^4\) hinders the quality and efficiency of clinical research,\(^5\) yet the contorted regulation researchers must now follow has not made research any more ethical. Similar concerns have been expressed in the US.\(^6\) ‘The great irony is that this regulation occurs at the same time that governments are pouring additional investment into research (over £3.3 billion has been promised for 2007–08 in the UK alone).’\(^7\)

On the other hand, it would be naive to overlook the heavy involvement of a profit-motivated industry.\(^8\) This has led other commentators to question the extent to which research brings about real benefits for patients and the criteria on which research agendas are set.\(^9\) Furthermore, they point to continued instances of trials gone awry that are reminders of the difficulties and risks surrounding scientific progress.\(^10\)

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The shameful history of research during the mid-part of the twentieth century also warns against a cavalier approach.\textsuperscript{11}

At a time when the tensions over research are particularly acute, it is important to reflect carefully upon the implications of new legal developments. One of the laws at the centre of the controversy is Directive 2001/20/EC (‘the Clinical Trials Directive’ or ‘CTD’).\textsuperscript{12} The CTD, which came into force on 1 May 2004, is now, by and large, implemented in all national jurisdictions.\textsuperscript{13} It was intended to harmonise the multifarious laws, regulations and administrative provisions of the Member States which relate to good clinical practice in the conduct of drug trials. In doing so, it was also supposed to support research, to facilitate European competitiveness and to protect participants. These goals were to be achieved while facing the constraints of European law-making, diverse moral views amongst Member States, parallel processes by the Council of Europe,\textsuperscript{14} strong lobbying from the pharmaceutical industry and limited input from the public sector research community. It was far from easy to arrive at clear and justifiable laws, and it is remarkable that the framers achieved as much as they did. But as one might expect, the CTD has a number of problems.

This article considers, in particular, Article 5 of the CTD which relates to research involving incapacitated adults (‘IAs’), meaning adults who are incapable of giving legal consent.\textsuperscript{15} It examines the

\textsuperscript{12} Directive 2001/20/EC on the approximation of the laws, regulations and administrative provisions of the Member States relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use (OJ L 121/34; 1 May 2001).
\textsuperscript{14} The Council of Europe agreed a Convention on Human Rights and Biomedicine in Oviedo in 1997 (‘Oviedo Convention’). Article 17 relates specifically to research with IAs. The Council subsequently worked on an Additional Protocol (‘Additional Protocol to the Oviedo Convention’) that addresses research involving IAs in more detail. It was finally agreed in 2005. Given that the majority of European Member States have ratified the Convention and the Additional Protocol bears a close resemblance to the Declaration of Helsinki, it is remarkable that Article 5 of CTD differs in striking ways: see below Section II-B and III-A (on clinical equipoise), Section III-B (on permitted investigations) and Section III-D (on emergency research).
\textsuperscript{15} In practice, it can be difficult to establish whether an adult is capable of giving legal consent. For reasons of space this issue is not discussed in this article. See generally: M. Gunn, ‘Decision-making Capacity’ (1999) 7 \textit{Med.L.Rev} 269–306; British
legal, ethical and practical difficulties countries could face after transposing Article 5 and proposes some solutions.

An issue that runs throughout the article is the need to reconcile two important regulatory goals: first, the importance of protecting IAs from the harm, distress and rights infringements that research could cause; and, second, the importance of stimulating research to ensure the future well-being of the IA population. At times it may seem that this article is more heavily weighted on the latter, but this is not because we disagree with the importance of protecting IAs.\footnote{In fact, some of our recommendations would strengthen the protection of patient-subjects: see Sections II, III-A, III-C, III-E.} Nor should it be taken as a signal that our arguments are predicated on utilitarian ethics (on this, see Section IV). It is, simply, that we believe readers from medico-legal backgrounds have a good understanding of the cognitive- and communicative-vulnerability of IAs,\footnote{See references \textit{op.cit.}, n.15.} but are considerably less familiar with the nature and importance of research.\footnote{Background literature: Plomer, \textit{op.cit.}, n.10, 43–65; J. McHale, ‘Clinical Research’ in A. Grubb (ed.), \textit{Principles of Medical Law} (2004) 853, 869–889; BMA, \textit{op.cit.}, n.15; P. Lewis, ‘Procedures that are Against the Medical Interests of Incompetent Adults’ (2002) 22 \textit{Oxford Journal of Legal Studies} 575–618; J.K. Mason \textit{et al.}, \textit{Law and Medical Ethics} (2002) 571–593; P. Moodie, M. Wright, ‘Medical Research and Alzheimer’s Disease: A Study of the Hazards of Conducting Research on the Incompetent Patient’ (1997) 2 \textit{Medical Law International} 291–313; D. Giesen, ‘Civil Liability of Physicians for New Methods of Treatment and Experimentation: A Comparative Examination’ (1995) 3 \textit{Med.L.R.} 22–52.}

The need for special medical research programmes involving IAs is real and profound. Not only is research necessary to help identify, understand and manage the unique diseases and conditions which affect people with mental illness, intellectual disability, age-related illness and critical conditions, it is also necessary to address the atypical effects of standard therapies on their bodies. The poor evidence base, the frequency of negative outcomes and the lack of specific therapies suggest that this research should be regarded as a public health priority. To deny IAs the benefits of medical research through unduly cautious research regulation is irresponsible; not kind nor caring. It condemns the population of IAs to poor quality care.

At present, we know little about how drugs standardly used in legally competent patients such as anti-dementia medication, mood stabilisers, anti-psychotics and anti-convulsants affect the intellectually disabled or...
There is much uncertainty about the clinical utility and side effects of drugs used to stabilise or treat mental illness. We have no specific treatment for 97 per cent of people who suffer from a stroke. More than 50 per cent of people who suffer from severe head injury die or remain seriously disabled for the rest of their lives, and more than 90 per cent die following an out-of-hospital cardiac arrest. Research to develop and test drugs, devices and new therapeutic strategies could significantly change this. Research has already had a major impact on new treatments and distinguishing safe from unsafe clinical instincts. For example, in the field of critical illness, investigators found a 6 per cent reduction in mortality from severe sepsis using activated protein C, a 9 per cent improvement in survival with better artificial ventilation strategies in respiratory failure, a 10 per cent improvement in survival with better artificial ventilation strategies in respiratory failure.

19 The drugs produce atypical responses due to differences in brain development and maturity. For instance people with Down’s syndrome have a high risk for developing Alzheimer’s disease with prevalence rates reaching 50% as early as 50–60 years of age. Small trials of anti-dementia medication have shown some benefit but also the possibility of some increase in confusion. It is increasingly important to establish whether these medications are beneficial in this client group and whether side-effects are similar or different. It also seems that the progression of dementia may be different in the general population compared with those with Down’s syndrome who have Alzheimer’s disease, which itself warrants further study; Correspondence A. Holland, Professor in Developmental Psychiatry, University of Cambridge (11/05/2006).


21 Only 3% receive tissue plasminogen activator. The remaining 97% receive no specific therapy because t-PA must be administered within a few hours and is currently associated with dangerous side effects. Research is needed to find safe and practical therapies for these patients: A. Rogalewski et al., ‘Toward a Multinodal Neuroprotective Treatment of Stroke’ (2006) 37 Stroke 1129–1136.


sugar control in critically ill patients, and a significant improvement in neurological outcome following cardiac arrest with the use of mild hypothermia. The CRASH trial further demonstrates the impact such research can have in clinical care. The results of this trial (a randomised placebo-controlled trial involving 10,000 IAs) halted the 30-year old practice of using corticosteroids in the treatment of traumatic head injury when the researchers discovered that these drugs increased the risk of death by 1–2 per cent. Thousands of lives will be saved as a result.

B. The Clinical Trials Directive

The 24 articles and 19 recitals that make up the CTD introduce a wide range of important and interesting provisions into European law. They include rules requiring:

(i) Research to be ‘sponsored’ by an organisation that accepts responsibility for compliance with the Directive;
(ii) Reports on adverse and serious adverse events to be submitted to the authorities, and official guidance on the form of these reports;
(iii) Good quality manufacturing of test drugs (including imported test drugs);
(iv) Applications for trial authorisation to be submitted to competent authorities in Member States prior to the commencement of a trial;
(v) Special labelling of test-drugs.

31 E.g. CTD Articles 9, 10.
32 CTD Articles 16, 17, 18.
33 CTD Article 13.
34 CTD Article 9.
35 CTD Article 14.
(vi) The appointment of inspectors in each Member State to verify compliance with the CTD;\textsuperscript{36}
(vii) The suspension of trials which no longer meet the obligations;\textsuperscript{37}
(viii) The establishment of a new European clinical trials database (EudraCT) with information shared by Member States and sponsors (both positive and negative findings);\textsuperscript{38}
(ix) Substantial amendments, completion and termination of trial protocols to be notified to authorities;\textsuperscript{39}
(x) Insurance cover for harms caused as a result of research;\textsuperscript{40}
(xi) Data protection;\textsuperscript{41}
(xii) Independent ethics review by committees in each Member State in which the trial takes place;\textsuperscript{42}
(xiii) Greater procedural efficiency from authorities and ethics committees;\textsuperscript{43}
(xiv) Informed consent from participants;\textsuperscript{44} and
(xv) The risks to participants and anticipated benefits of research to meet particular ratios.\textsuperscript{45}

Another key feature is that the CTD is limited to a defined subset of clinical trials. It covers trials with pharmaceuticals, but not medical devices, and then only those drug trials that study the safety or efficacy of the drug. It does not cover mechanistic studies which probe biological mechanisms.\textsuperscript{46} Each of these facets of the CTD will have far-reaching implications, both beneficial and problematic, for the future regulation of medical research. They all warrant close study, but in view of space constraints, our discussion will be confined to the last four points, which are distinctly important for research involving IAs.

We also limit our comments about the history of the CTD to two brief points. The first point is that the CTD was characterised by a long gestational period, lasting more than ten years. This hints at the complexity, importance and controversy of the issues; it has also

\textsuperscript{36} CTD Article 15.
\textsuperscript{37} CTD Article 12.
\textsuperscript{38} CTD Article 11.
\textsuperscript{39} CTD Article 10.
\textsuperscript{40} CTD Article 3.
\textsuperscript{41} CTD Article 3.
\textsuperscript{42} CTD Article 6.
\textsuperscript{43} E.g. Ethics committees and competent authorities have a maximum of 60 days to make a decision on the acceptability of a clinical trial protocol: Articles 6, 9.
\textsuperscript{44} CTD Articles 3, 5.
\textsuperscript{45} CTD Articles 3, 4, 5.
\textsuperscript{46} CTD Article 2(a), 2(c) and 2(d).
proven problematic. Just as soon as the European authorities reached agreement, even before Member States implemented the standards, officials tend to be already working on further regulatory developments.\(^{47}\) This means there is still much to be done to achieve a sense of regulatory stability and coherence, and to explain to people at the coalface how research is regulated. The second point is that the CTD’s history explains some of the social forces that led to the problems we identify later in this article. Although the official documents routinely stated that the intention was to protect participants, whilst facilitating high-quality research and a competitive industry, it is difficult to shake the feeling that the voices of industry received more than due attention. The principal instrument on which the Directive was based was not the Declaration of Helsinki (approved by the World Medical Association),\(^{48}\) but the European Good Clinical Practice (GCP) guidelines,\(^{49}\) which are based on the ICH–GCP. The ICH process (which stands for International Conference on

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47 One of the initial steps was to agree a set of guidelines on Good Clinical Practice for Trials on Medicinal Products in the European Community (GCP) in July 1990. However, this was considered inadequate because the guidelines themselves had no legally binding effect, Member State laws could displace the standards, the standards were not democratically accountable, the power to carry out inspections to ensure compliance with GCP was unclear, and there were no penalties for breaches. An article proposing a binding Directive was circulated in 1991 even before the GCP guidelines had been implemented: D. Sprumont, ‘Legal Protection of Human Research Subjects in Europe’ (1999) 6 European Journal of Health Law 25, 33. The CTD echoed this history. Once agreed, and even before Member States had transposed it, the Council and Parliament were at work preparing further Directives to expand on the meaning of ‘good clinical practice’ and ‘good manufacturing practice’. These were agreed in 2003 (‘the Good Manufacturing Directive’ 2003/94/EC) and 2005 (‘the Good Clinical Practice Directive’ 2005/28/EC). Another example is that UK government implemented the CTD in 2004, but recognised the need to amend aspects of the Regulations which restricted emergency research within a year: see Section III-D and the Medicines for Human Use (Clinical Trials) Amendment Regulations 2006.

48 World Medical Association, Declaration of Helsinki: Ethical Principles for Medical Research Involving Human Subjects (1964). The Declaration was first published in 1964 in an attempt to extend and remedy the problems of the Nuremberg Code 1949 (e.g. the Code, prepared by lawyers, inadvertently prohibited all research with incompetent adults). Over the years, the Declaration has been amended several times most recently in 2000 and in Notes of Clarification in 2002 and 2004. It has been described as ‘the most widely accepted guidance worldwide on medical research involving human subjects’: see generally D. Human and S. Fluss, ‘The World Medical Association’s Declaration of Helsinki: Historical and Contemporary Perspectives’ (2001, fifth draft) http://www.wma.net/e/ethicsunit/pdf/draft_historical_contemporary_perspectives.pdf.

Harmonisation)\textsuperscript{50} is led by pharmaceutical industry associations. It aims to negotiate guidelines on the authorisation of medicines acceptable to industry and the three major agencies (the US Food and Drugs Administration (FDA), the European Medicines Agency (EMEA) and the equivalent Japanese authority) to lessen the barriers to global trade.\textsuperscript{51} Furthermore, the CTD was drafted not by units in the Commission responsible for health or human rights (e.g. the Research Directorate-General (DG)), but by the DG for Enterprise and Industry. This is not to say that business ignores the importance of ethical conduct—the ICH–GCP guidelines have been one of the most important controls on unethical research—but the financial interests of business can skew conclusions. This may explain the compromises that fail to find a coherent balance between research and subject protection in areas of low profitability (e.g. research involving children and IAs) and academic research (e.g. emergency research).

The changes brought about by the CTD that are of most concern to research with IAs are set out in Article 5. It stipulates that when adults are incapacitated,\textsuperscript{52} their inclusion in a trial shall be allowed only if the research meets the general protections for subjects and nine further conditions. The general protections are listed in Article 3. They prohibit clinical trials unless:

(i) [the] risks and inconveniences have been weighed against the anticipated benefits for the individual trial subject and other present and future patients... [and the]... benefits justify the risks...;

(ii) the trial subject or, when the person is not able to give informed consent, his legal representative has had the opportunity in prior interview... to understand the objectives, risks and inconveniences of the trial...;

(iii) The rights of the subject to physical and mental integrity, to privacy and to the protection of the data concerning him... are safeguarded;

(iv) the trial subject or, when the person is not able to give informed consent, his legal representative has given his written consent...;

\textsuperscript{50} More fully, the ‘International Conference on Harmonisation of Technical Requirements for the Registration of Pharmaceuticals for Human Use’.


\textsuperscript{52} Note that the Article 5 conditions do not apply where an individual gives or refuses consent prior to the onset of their incapacity. This is assumed throughout the rest of the article.
(v) the subject may without any resulting detriment withdraw from the clinical trial at any time . . .
(vi) provision has been made for insurance or indemnity to cover the liability of the investigator and sponsor.

The nine additional restrictions applicable to trials involving IAs are listed in Article 5. They prohibit trials involving incapacitated adults unless:

(i) the informed consent of the legal representative has been obtained. [The] consent must represent the subject’s presumed will and may be revoked at any time, without detriment to the subject;
(ii) the person not able to give informed legal consent has received information according to his/her capacity . . . [about] the trial . . .;
(iii) the explicit wish of a subject [i.e. the incapacitated person] who is capable of forming an opinion and assessing this information to refuse participation in . . . the clinical trial at any time is considered by the investigator or where appropriate the principal investigator;
(iv) no incentives or financial inducements are given except compensation;
(v) such research is essential to validate data obtained in clinical trials on persons able to give informed consent or by other research methods and relates directly to a life-threatening or debilitating clinical condition from which the incapacitated adult suffers;
(vi) clinical trials have been designed to minimise pain, discomfort, fear . . . [and are] constantly monitored;
(vii) the ethics committee, with expertise in the relevant disease and the patient population concerned or after taking advice in clinical, ethical and psychosocial questions in the field of the relevant disease and patient population concerned, has endorsed the protocol;
(viii) the interests of the patient always prevail over those of science and society.
(ix) there are grounds for expecting that administering the medicinal product to be tested will produce a benefit to the patient outweighing the risks or produce no risk at all.

C. Controversy

In many respects, the CTD was welcomed by industry investigators, academic investigators and organisations representing subjects. It helps restrict useless or exploitative research and facilitates cross-border pharmaceuticals research, both of which are important achievements. Prior to
the CTD, industry and academic researchers were inhibited and confused by patchy legal provisions across Europe. The English approach, based on common law and the test of best interests, was considered particularly confusing, and not only by Continental researchers.\textsuperscript{53} The CTD also heralded a radical change in the enforceability of research subject protections. Previously protections were unclear and, to a large extent, not legally binding. For example, in many Member States, there was no legal requirement to seek ethics committee approval, to make others aware of adverse reactions, or to consider insurance cover. This made it difficult for officials or research subjects to enforce subject protections. The CTD has also assisted small Member States and those preparing for EU accession, which struggled to identify appropriate benchmarks amid the diversity of laws. Most importantly, the CTD has helped reassure Member States that research involving IAs is justifiable and compatible with human rights, provided it meets certain conditions.

That said, there is also much dissatisfaction with the CTD. It involved such highly composite goals—simplification, harmonisation, protection of public health, protection of research participants, fostering an internal market in pharmaceuticals and establishing a legal foundation for principles of good clinical practice—that some issues were lost in the scrum. Other authors have noted that ‘unless the Directive is implemented sensitively and pragmatically, there will be onerous new responsibilities’ that simply cannot be met.\textsuperscript{54} They have drawn attention to the effect the CTD will have on non-commercial research, the lack of

\textsuperscript{53} Under English common law, a researcher was potentially liable in battery or negligence for acts done to an IA which normally require consent if those acts were not consistent with their ‘best interests’ and the Bolam principle; the assent of the IA’s spouse or family member was not lawful justification. This was widely interpreted to mean that the anticipated benefits of research (direct or indirect) needed to outweigh the anticipated disbenefits. Accordingly, so-called ‘non-therapeutic research’ was not considered to meet the best interests test (see Law Commission, \textit{Mental Incapacity} (HMSO, 1995); BMA, \textit{op.cit.}, n.15). Thus, the common law excluded a variety of research regarded as ethical by the profession including research with healthy IAs which involves no more than biometric measurements, observational studies in nursing homes, genetic studies of adults with learning disabilities and other epidemiological studies involving blood, saliva or tissue samples. That said, the standard interpretation had not been tested in a case involving medical research (as distinct from innovative therapy where the best interests test can be applied straightforwardly: \textit{Simms v. Simms} [2003] Fam 83). Thus many chose to overlook or to comply creatively with prevailing legal rules. In future, the Clinical Trial Regulations 2004 which transpose the CTD will govern clinical drug trials involving IAs, and the Mental Capacity Act 2005 will cover other research where consent is normally required. Neither requires the best interests test to be applied in situations of research. Both state that the interests of the individual outweigh those of science and society and require (\textit{inter alia}) consent from legal representatives.

\textsuperscript{54} Academy of Medical Sciences (2003), \textit{op.cit.}, n.3, 6.
clarity around some requirements, the regulatory burden,\textsuperscript{55} regulatory creep,\textsuperscript{56} limited input by academic and public sector organisations,\textsuperscript{57} and persistent heterogeneity.\textsuperscript{58} The difficulty is that the Directive implicitly assumes that the purpose of performing a clinical trial is to produce data to support an application for market authorisation, whereas many trials are conducted by the non-commercial sector simply to improve medical practice. This sector does not have the same resources or business models to meet the costs of the new requirements. Trials involving IAs are particularly affected. They routinely take place as academic studies, as the commercial sector finds them difficult and less remunerative.\textsuperscript{59} Fortunately, the criticisms have been noted and some changes are evident in the 2005 GCP Directive.\textsuperscript{60}

In this article, we draw attention to a variety of other problems that have received less attention and that specifically affect research involving IAs. This is all the more disappointing because, prior to the CTD, each problem had been recognised and steps had been taken to address it in other instruments, including recent revisions of the Helsinki Declaration, the ICH–GCP, and high-profile reports by the National Bioethics Advisory Commission (NBAC) in the United States.\textsuperscript{61} The problems

\textsuperscript{56} Some Member States have applied similar strict principles to research based on human tissue, health records and pathophysiological observations despite the lower risks: Lemaire et al., (2005), op.cit., n.13.
\textsuperscript{59} A special regulation has been proposed to facilitate commercial sector research on medicines for children. A similar step has yet to be taken for incapacitated adults although the problems are comparable in many respects: Commission Communication regarding the Council Common Position on the paediatric regulation COM(2006) 118 (13/03/06).
\textsuperscript{61} US National Bioethics Advisory Commission (‘NBAC’), Research Involving Persons with Mental Disorders That May Affect Decisionmaking Capacity (1998); NBAC, Ethical and Policy Issues in Research Involving Human Participants (2001). The reports came about as a result of gaps, uncertainties, heterogeneity and inconsistent rulings in US law in the 1980s and 90s. They are more detailed and persuasive than any report undertaken in Europe.
have not only resurfaced as a result of the CTD, but are at risk of being entrenched in European law.62

II. CONCEPTUAL FOUNDATIONS

We have already highlighted the strength of the industry lobby as one of the reasons for the problems in the CTD. Another cause is the widespread conceptual confusions about research that persist, despite literature by doctors and ethicists calling them into question. Medico-legal literature is one of the main sources of the confusion. It has not grasped why the distinction between research with and without the potential for direct benefit to the individual (more colloquially known as ‘therapeutic’ or ‘non-therapeutic’ research) is flawed. Second, legal literature rarely describes the concept of clinical equipoise, let alone its importance. We attempt to clarify these points before examining the problems of the CTD in detail in Section III. A further confusion in legal literature is the view that so-called ‘non-therapeutic research’ (i.e. that which does not benefit the individual IA directly) is unethical, unless one supports a specious kind of utilitarianism. We address this myth in Section IV.

A. Defining ‘Research’
(or The Need to Suppress the Distinction between Therapeutic and Non-therapeutic Research)

The difference between research and medical practice and its implications for regulation is frequently discussed in medical literature, but is less familiar to lawyers, policymakers and ethics committees. Whereas the standard dichotomy in legal circles is between therapeutic research and non-therapeutic research—or research with and without direct benefits for the individual—a more helpful taxonomy distinguishes between: (a) standard medical treatment, (b) innovative medical treatment and (c) research. This was recognised as long ago as 1979 by the US National Commission for the Protection of Human Subjects of Biomedical and Behavioural Research.63 In this taxonomy,
research is defined as a systematic ‘activity designed to test an hypothesis, permit conclusions to be drawn, and thereby to develop or contribute to generalizable knowledge (expressed, for example, in theories, principles and statements of relationships)’. It differs from the other two categories for one reason: in standard and innovative treatment, the activity is designed to benefit a specific individual. Doctors customize therapy according to the patient’s personal or situational idiosyncrasies. Their primary aim is to restore the patient’s health as quickly as possible. In research, the professionals’ goals are fundamentally different. Their primary aim is to benefit a broader population by producing reliable, statistically significant information. To do so, investigators treat the individual’s specific preferences or subtle needs as subordinate to the task of gathering data systematically, usually according to a protocol with hypotheses, controls, definitions, set procedures and endpoints. This significantly changes the relationship between health professionals and the patient, making it appropriate for the law to scrutinise the relations between the two more closely.

The popular dichotomy between ‘therapeutic research’ and ‘non-therapeutic research’ emerged after World War II in an effort to avoid repeating abuses committed during the wars. The assumption was that research combined with patient care could be categorically considered more ethical, as the patient benefited and physicians were guided by the patient’s interests. This thinking is still engrained in legal literature and European laws, but is widely recognised as flawed in other documents, including the amended Helsinki Declaration and NBAC reports. The latter are by no means advocating no potential direct benefit to the individual provided the burdens and risks of research did not exceed a certain level.

64 Belmont Report, op.cit., n.63.
65 For example, the patient may not have his drug dosage raised or lowered even when the change might suit him; he may be required to forgo helpful medications during a ‘washout period’; he may be denied drugs that treat side effects such as decongestants or sleeping pills; or he may be required to remain in hospital for a longer period.
68 NBAC recommended that when assessing risky procedures one should separately assess those risks that present a prospect of direct medical benefit and those that do not: ‘Although these categories may seem to imply a distinction between ‘therapeutic’ and ‘non-therapeutic’ [research], that is not the case and, in fact, is a serious misconception’: [NBAC (1998), op.cit., n.61, 8]. It expanded on this in its 2001 report: ‘In general, each component of a study should be evaluated separately, and its risks should be both reasonable in themselves as well as justified by the potential benefits
abusive research or a cold-hearted medical profession but rather some ‘clear thinking about research risk’. 69

The principal problem is that the term ‘therapeutic research’ blurs the distinction between therapy and research, encouraging people to think that the research itself is therapeutic, even when honestly warned that it is designed to serve the public interest, not the individual. The more accurate view is that while research is often combined with clinical care and other beneficial activities (as in research designed to evaluate a therapy), it is the clinical elements that benefit the patient–participant, not the research as such. However, category conflation persists because society uses the term ‘research’ in other loose ways—for example, we refer to a set of clinical and research activities being a ‘research protocol’ and to heroic efforts to solve a patient’s disease as ‘experimental research’ (when in fact it is innovative therapy). The inertia is compounded because it is sometimes difficult to demarcate public-spirited research from clinical concerns. For example, doctors are often inquisitive when they administer treatments; aspects of a research protocol may be relaxed to reduce the burden of research given an individual’s personal idiosyncrasies (e.g. an individual might be interviewed at a different time of the day if they are too tired); different motivations can explain case study review; there may be no clear moment when a clinician begins research (particularly when it involves records and tissue) and many patients do in fact benefit from research (e.g. those randomised to the treatment which turns out to be better, or those who receive more attentive monitoring and follow-up from investigators). 70 But despite the difficulties, it is possible and important to discipline our language so that the term ‘research’ reflects the concept that the physician does something to a patient that is not intended to benefit that patient, but to gather knowledge to assist other patients.

Instead of attempting to classify an experiment as ‘therapeutic research’ or ‘non-therapeutic research’, a better approach, outlined by Professor Weijer and his colleagues, is to analyse it in terms of ‘therapeutic components’ and ‘research components’. 71 This has been

to society or the participants. Potential benefits from one component of a study should not be used to justify risks posed by a separate component of a study’; NBAC (2001), op.cit., n.61, recommendation 4.1.


termed ‘component risk analysis’. Therapeutic components are the activities researchers do which they know (according to prior evidence) may prove of therapeutic benefit to the particular individual, and which could be undertaken ethically and lawfully by a doctor treating a patient. The investigators can claim ‘therapeutic warrant’ to justify these actions. These actions might take place whether or not a scientific hypothesis was being tested. Typical examples include the provision of a drug that may improve a condition and routine monitoring. Research components are the activities that are done without any likelihood of benefit for the patient. These activities would not occur save for the fact that the doctor is trying to produce generalisable knowledge. Typical examples include randomisation, fixed dosage and special monitoring and observation. What appears to be a singular ‘research programme’ will often consist of a mix of components: some therapeutic and some research. Rather than call this ‘therapeutic research’ it is better to refer to it as ‘research combined with therapy’ or, better still, ‘research with therapeutic components’. An investigation that consists of therapeutic components only (i.e. components delivered with therapeutic warrant) is properly called ‘innovative therapy’. Investigations that consist purely of research components (i.e. components intended to benefit science and society) might be referred to as ‘non-therapeutic research’ or ‘research without therapeutic components’.

To lawyers, component risk analysis may seem unnecessarily complicated. Its value lies in the fact that it enables the activities a researcher carries out with therapeutic warrant (i.e. with a reasonable belief that his actions may benefit the individual patient) to be analysed separately.


72 A placebo control should be regarded as a special kind of therapeutic component. (Correspondence P. Miller, 14/05/06).

73 Sometimes a procedure may appear to be geared both to therapy and research. For example, a single blood sample might be analysed for both clinical and research purposes, or a doctor might reflect upon the implications of a patient’s therapy for future patients. These situations are simple enough to resolve. If the physician’s conduct is constrained by the individual’s well being so that his dual purpose presents no conflict of interest and there is a reasonable expectation that what he is doing may benefit the specific IA, the activity is a therapeutic component.

74 Typical examples of research components include randomisation (particular patients might prefer treatment A or B), enrolment (this takes up the subject’s time and probably involves them giving over additional personal information), delivery of a set dosage (ordinarily the doctor would adjust the dosage if it seemed to suit the patient), and special monitoring (the subject might be asked to provide special blood or urine samples, to return to hospital for follow up tests or in some circumstances to be X-rayed, etc.)
from the things the researcher does that are solely intended to serve the public. The risks associated with activities of the former kind are not special; they occur every time a patient receives treatment from a doctor. Aside from issues of consent, the physician-researcher must simply demonstrate two things: that the risks are compatible with normal clinical standards of care and that he has observed the principle of clinical equipoise (see Section II-B). The risks associated with activities of the second kind are special. Here the researcher uses the patient in order to serve a wider population and, hence, special mechanisms of oversight are warranted to ensure that the patient is not exploited inappropriately.

The conventional classification of ‘therapeutic research’ and ‘non-therapeutic research’ distinguishes risks in a less sophisticated way. The category ‘therapeutic research’ assesses the legitimacy of research by conflating all the associated risks—both clinical (for the individual) and research (for the public)—into a single net aggregate, regardless that some benefit the individual whereas others do not. Calling the research ‘therapeutic’ also suggests that the patients’ health is likely to be advantaged if they participate in the research (the ‘therapeutic misconception’) whereas, in fact, they could often enjoy the same benefits, plus more personal tailoring, if they declined to participate in the research and asked for the therapy the doctor thought was best for their condition. A further problem with the conventional classification is that it makes ‘non-therapeutic’ research seem particularly exploitative because it has no associated ‘therapy’. In fact, in situations of true ‘non-therapeutic research’, the individual probably has no need of therapy and the risks undertaken for the public’s benefit may be very minor. ‘Non-therapeutic research’ often consists of observation, blood tests or analysis of health information. So-called ‘therapeutic research’ might involve rapid drug washouts, PET scans, lumbar punctures, bone marrow biopsies, placebos that leave the illness untreated, untested cocktails of drugs, or challenge studies in which symptoms are provoked or a condition allowed to worsen. Indeed, most research-related deaths occur in situations where research is classified as having ‘direct benefit for the subjects’ because aggregate risk analysis does not pressure physician-researchers to minimise research risks. Aggregate risk analysis also tends to preclude research when the patient suffers from a condition for which there is no effective therapy, yet the research

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75 That is, the physician-researcher must demonstrate that the risks associated with the clinical components are equivalent to the risks that doctors normally undertake in clinical care—the anticipated benefits should outweigh the risks.


risks are minimal.\textsuperscript{78} This can be problematic for research into terminal illness. In short, the value of ‘component analysis’ is that it enables the incremental risk associated with the search for scientific knowledge to be distinguished and regulated differently from risks associated with attempts to improve the patient’s personal situation.

**B. Clinical Equipoise**

A further point to explain is the concept of clinical equipoise. Although rarely described in legal literature,\textsuperscript{79} it is highly familiar to clinical researchers and medical ethicists. At its simplest, it can be described as a state of honest doubt as to which of two clinical interventions is more beneficial for the patient. In more formal terms, it concerns the ethics of withholding particular treatment from a patient to gather statistically reliable information. The principle of clinical equipoise stipulates that a patient should not be involved in a randomised-controlled trial—meaning a trial that randomly assigns patients to two or more treatments—unless there exists a state of honest, professional disagreement in the community of expert practitioners\textsuperscript{80} as to the preferred treatment. The rationale for observing clinical equipoise is that it ensures that patients involved in studies that aim to answer scientific questions are not prescribed treatments that are known to be less effective than some other treatment for their condition; but where there is uncertainty, it is not unethical for a doctor to give that treatment. In practice, clinical equipoise tries to ensure that patients involved in medical research receive competent care by placing constraints on the selection of control arms in clinical trials.

The ethical requirement for equipoise is said to flow from doctors’ obligations as members of a caring profession.\textsuperscript{81} The moral obligation to take care of a patient binds all doctors involved in research insofar as they combine research with clinical care. It also binds those who contemplate enrolling their patients in the research. Although research activities differ from clinical work, these people carry out their work as doctors

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\textsuperscript{78} In these scenarios, an aggregate risk analysis would find no clinical benefit to weigh against the research risk so the risk ratio would be negative.

\textsuperscript{79} For one exception: I. Kennedy, ‘Consent and Randomized Controlled Trials’ in I. Kennedy (ed.), *Treat Me Right—Essays in Medical Law and Ethics* (1992) 213. The principle is also mentioned obliquely in: Mason et al., *op.cit.*, n.18, 579.


\textsuperscript{81} For similar reasons, the duty might extend to other health professionals, but it is typically associated with the people controlling a research project and the patient’s clinical care (*i.e.* the doctors).
and should continue to observe their professional duties to take reasonable care not to harm a patient. This accords with obligations of beneficence, professional virtues and legal duties of care. From a practical perspective, it could also be said that a rational patient or proxy is unlikely to agree to a protocol unless it meets clinical equipoise.

One of the most significant implications of clinical equipoise is that the outcomes of a research project that meets clinical equipoise will be highly uncertain. The community of physicians will genuinely not know whether a patient will benefit from being in the trial. If a patient does not participate, they will receive standard treatment; if they do, they will be randomised to an arm of the trial whereby they will either receive standard treatment or the comparison treatment which is not known to be better or worse. Until the trial is completed, it will not be known which of the treatments is better, and it will be impossible to predict whether the patient would be worse off for participating in the trial.

To appreciate how the principle of equipoise works in the research context, it is important to consider it alongside the idea of component risk analysis. Weijer explains that it is the therapeutic components of a randomised-controlled trial that should meet the standards of clinical equipoise. The research components are analysed separately. Clinical equipoise ensures ‘a rough parity in terms of benefit, harm, and uncertainty between the procedures that patients would receive as a part of clinical practice and therapeutic procedures [he receives] in a clinical trial.’ This means the patients’ therapeutic goals are no better and no worse off than if they did not participate in the research. The additional risks they face due to the research components of the trial are the result of their bodies being used to answer scientific questions and should be monitored more closely.

The concept of equipoise is not free from difficulty or controversy. One question is whether the principle recommends that participants assigned to the control group should be given ‘best known’ methods

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82 An explanation for this obligation is given below with reference to work by T. Ackermann and O. O’Neill: see below Section IV-C and IV-D.
83 In some jurisdictions the principle might also be argued to be a fiduciary obligation of a doctor: P. Miller and C. Weijer, ‘Fiduciary Obligation in Clinical Research’ (2006) 34(2) J.L.M.E. 424.
85 This is usually determined by the doctor’s intuitions, the conventions at the institution where he or she works, or the resources at the patient’s disposal.
86 Weijer (2004), op.cit., n.69, 86.
87 By the individual where possible (through mechanisms of consent) and other persons expert in risk analysis and research ethics.
of care, objectively ‘competent’ care, ‘proven’ methods or methods ‘currently accepted as standard’. A practical problem is the subjectivity involved in assessing whether two treatments are equivalent and identifying the ‘medical community’. Evidence about their outcomes is likely to be patchy and open to different views and can be difficult to substantiate at the individual level. Another issue is how much disagreement within the profession certifies genuine uncertainty. These sorts of arguments point to the difficulty of implementing a requirement for clinical equipoise. They are not reasons to jettison it.

In contrast, Miller and Brody stiffly assert that the principle should be rejected altogether. In their view, the principle of clinical equipoise is an unnecessary and unhelpful restriction because it limits the use of inactive controls (placebos and inactive surgery). Conclusions must accordingly be drawn in comparison with active controls, which makes it considerably more difficult to reach clear, incontrovertible, scientific conclusions. Miller and Brody instead argue that a doctor can legitimately ask a patient to risk their personal well being to help answer scientific questions. If the patient (or their proxy) decides to accept the risk, the doctor’s obligation to provide competent care comes to an end. The obvious problem with this argument is that it assumes that patients have the expertise to weigh the risks accurately, and that they realise that the responsibility for risk assessment has been delegated entirely to them—not only the decision to enter the

88 Contrast the Helsinki Declaration which requires ‘best methods’ save in exceptional circumstances, and the Additional Protocol to the Oviedo Convention which requires ‘proven methods’.
89 This is relevant not only to the legitimacy of starting the trial, but also the criteria for when it should end.
91 Particular patients may have personal preferences which tip the balance in favour of one treatment. For instance, some women may be opposed to therapies that affect their body image such as mastectomy or hair loss: S. Botros, ‘Equipoise, Consent and the Ethics of Randomised Clinical Trials’ in P. Byrne (ed.), Ethics and Law in Health Care and Research (1990) 9, 16.
94 In an effort to make their case, Miller and Brody argue that the principle of clinical equipoise fails to appreciate the distinction between treatment and research, but in doing so they overlook the system of component analysis put forward by Weijer, op. cit., n.69. He and his co-authors are clearly cognisant of the distinction between research and therapy whilst joining others to advocate the importance of equipoise.
95 It is not clear which constraints beyond consent, if any, Miller and Brody would advocate.
trial, but also the decision when to break off participation. The view embedded in the revised Helsinki Declaration is that the responsibility for the human subject must always rest with a medically qualified person and never solely with the subject of the research. The underlying argument is that patients are highly dependant on the expertise of doctors and that a patient’s decisional freedom is neither a plausible nor sufficient reason to deny patients proven therapy. This issue cannot, and need not, be resolved in full in this paper. In our view, it is clear that there is good reason to uphold the principle of clinical equipoise. If it is to be set aside, it should only be in exceptional circumstances.

A similar conclusion was reached in recent clarifications of the Helsinki Declaration. It states that a placebo-controlled trial should generally be used only in the absence of proven therapy. However, research may be ethically acceptable where proven therapy is available if there are compelling and scientifically sound reasons to think the research is necessary to determine the efficacy or safety of a medical method, or where the medical method relates to a minor condition and the patients receiving placebo will not be subject to any additional risk or serious or irreversible harm. The principle of clinical equipoise is also recognised in the Additional Protocol to the Oviedo Convention.

III. CRITICISMS

Having described the purpose of the CTD, its main provisions and certain epistemological foundations, we are now in a position to explain our criticisms and recommendations that pertain to Article 5.

A. Risk Assessment

As described, the purpose of research is to produce knowledge that can be generalised to improve the well being of individuals within the community. It may, however, at the same time be combined with activities that are intended to assist the patient. Accordingly, the purpose of research governance is not to guarantee benefits to individual research subjects, but to ensure that activities done with therapeutic warrant

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96 Amended Helsinki Declaration, Article 15.
97 Some have suggested that if Miller and Brody’s argument is accepted then an alternative safeguard against exploitation would be needed. Short of this, the argument should be rejected: L. Jansen and A. Closer, Look at the Bad Deal Trial: Beyond Clinical Equipoise (2005) 35 Hastings Center Report 29, 31–34.
98 Amended Helsinki Declaration, Note of Clarification on Paragraph 29 (2002).
99 It recognises fewer exceptions but requires only that the physician guarantee ‘proven methods’ rather than ‘best current methods’: Additional Protocol to the Oviedo Convention, Article 23(2).
meet the standards of clinical care, that groups are not excluded from
the benefits of medical research and that the risks associated with
research are carefully scrutinised so that society does not take undue
advantage of individuals. 100

Prior to the CTD, other European and international instruments went
some way towards resolving and harmonising these issues. They proceed
on the basis that individuals should be included in research only if the
ratio between risk and potential benefit is positive. 101 For example,
the Helsinki Declaration states that medical research should be con-
ducted only ‘if the importance of the objective outweighs the inherent
risks and burdens to the subject’. 102 Similarly, the Oviedo Convention
prohibits research unless ‘the risks which may be incurred by that
person are not disproportionate to the potential benefits of the
research’. 103 A problem, however, was that European instruments tena-
ciously clung to the flawed concept of research with and without indi-
vidual benefit. This has obscured the way risks and benefits should be
assessed. For example, the Oviedo Convention stipulates that research
must be regulated more strictly if it lacks ‘the potential to produce
real and direct benefit to (the IA’s) health’. 104 This is repeated in the
Additional Protocol to the Oviedo Convention. 105 National laws in
the Netherlands, Germany, Austria, UK and elsewhere reiterated this
idea, suggesting that research ‘with benefit’ (a confusion) is good
research and denigrating research that is not combined with clinical
care, even forbidding it many circumstances. France is one of the few
countries that has amended its law (the ‘loi Huriet’) to remove the dis-
tinction between research with and without individual benefit. The
CTD is a positive step forward because it has also avoided using the ter-
minology. Despite this, it has the potential to repeat and exacerbate
similar problems unless it is implemented in a nuanced fashion.

The relevant provisions of the CTD state:

Art 3(2)(a): ‘the foreseeable risks and inconveniences have been
weighted against the anticipated benefit for the individual trial subject
and other present and future patients . . . and the anticipated therapeutic
and public health benefits justify the risks’.

100 Ethical justifications for this stance are explained in more depth in Section IV.
101 See generally H. Silverman et al., ‘The European Union Directive and the Protection of
Incapacitated Subjects in Research: An Ethical Analysis’ (2004) 30 Intensive Care
Medicine 1723–1729.
102 Amended Helsinki Declaration Article 18.
103 Oviedo Convention Article 16(ii).
104 Oviedo Convention Article 17(1)(ii).
105 Additional Protocol to the Oviedo Convention Article 15(i).
Art 5(i): there must 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 risk at all’.

Article 3(2)(a) is a typical textual formula that encourages aggregate risk analysis. It offers little protection to an IA. It allows the risks of research to be offset by anticipated benefits of clinical care.\textsuperscript{106} In this case, it also allows the benefit to the public to outweigh any degree of risk to the individual. No mention is made of clinical equipoise, nor it is stated that the risks should be necessary, proportionate or minimised.

Article 5(i) is problematic in other ways. In particular, it is not clear how it can apply in circumstances of clinical equipoise. Constrained literally, it sets a risk:anticipated benefit threshold that requires an expectation that patients will benefit from the test-drug to an extent that outweighs the risks of not receiving the test-drug. Alternatively, there must be evidence to expect that the test-drug involves no risk (which is very rare). Since IAs not given the test-drug receive standard available treatment, the literal reading means there must be an expectation that the test-drug is better than standard available treatment or is risk free. This is highly problematic if physician-researchers observe clinical equipoise. In such situations, there is genuine uncertainty amongst the profession as to which treatment—test-drug or standard available treatment—is better.\textsuperscript{107} The uncertainty that is the very essence of clinical equipoise precludes a clear expectation that the test-drug is better than standard treatment or is risk free. Although a good trial is expected to be conclusive (meaning one arm of the trial is expected to have a better outcome),\textsuperscript{108} there is substantial uncertainty as to which of the two groups this will be.

It is difficult to know why the principle of clinical equipoise was overlooked in this way. One explanation is that those drafting the Directive were strongly influenced by the pharmaceutical industry which, preferring the ease of placebo-controlled trials, downplayed the importance of

\textsuperscript{106} The problems and irrationalities of aggregate risk analysis were explained above: Section II-A.

\textsuperscript{107} The phrasing is not as problematic for a physician-researcher who is more optimistic about the test-drug than the medical community. For instance, an individual investigator could honestly claim to observe the principle of clinical equipoise (it is measured against the views of medical community) whilst simultaneously expecting that the test-drug will be beneficial. This may absolve a few investigators from legal liability, but it will not absolve the majority (since, overall, the profession is uncertain whether the test-drug is better) and it does not resolve the difficulties of legal interpretation for research ethics committees or Member State authorities. The latter should adopt the objective stance of a reasonable hypothetical physician-researcher.

\textsuperscript{108} Except in equivalence trials where both arms are expected to have the same outcome.
clinical equipoise. The Helsinki Declaration was also going through a period of turmoil at the time. A form of words to describe acceptable risks compatible with clinical equipoise did not emerge until the work of NBAC, Weijer and the framers of the Additional Protocol to the Oviedo Convention gained currency.

Member States must now handle the deficiencies of Articles 3(2)(a) and 5(i) as best they can. One option is for investigators, Member States and ethics committees to ignore the principle of clinical equipoise when assessing the lawfulness of research with IAs. For instance, the words ‘grounds for expecting’ could be read as meaning that there is some chance that the test-drug will be better. It need not be certain or likely in the eyes of the medical community; just possible. A chance of roughly 25 per cent might suffice. However, this spurns the concept of clinical equipoise which, for reasons given in earlier sections would be unethical. Although criticisable, clinical equipoise performs an important function facilitating society’s trust in the medical profession, notwithstanding a strong research culture, and ensuring that the IAs assisting the scientific enterprise are not denied effective therapies. To reject the concept of equipoise would also be inconsistent with the Declaration of Helsinki (potentially causing problems when researchers reach the point of publication) and the Additional Protocol to the Oviedo Convention (which is binding in many Member States).

Another approach would be to alter the frame of risk analysis so that rather than compare the test-drug against standard available treatment, one compares it with no treatment. In other words, the researcher might assess the IA in their current sick state and ask, ‘what benefits and risks might the patient experience if I give them the test-drug as compared with a scenario where I do nothing?’ If the chances of the drug working are better than its risks, this will enable the researcher to conclude that the IA will benefit overall. However, such risk-framing can be highly disingenuous from the IA’s perspective. The question for his legal representative is not, ‘should nothing be done or should the IA be enrolled in the trial where he might receive the test-drug?’ The representative actually faces the question ‘should standard treatment be sought or should he be enrolled in a trial involving the test-drug?’ Similarly, the IA’s doctor faces the question, ‘should I advise this patient to seek standard treatment or that he enrol in the trial?’ It is far fairer to compare the test-drug against proven treatments that are standardly available in the health care system.

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109 In the same way that if one plucks a card from a full deck, there are ‘grounds for expecting’ the card selected will be a spade.

110 The issue is more controversial where proven therapies are expensive and hence not ordinarily available to research participants. The question is whether individuals
How then should Member States interpret and implement Article 5(i)? We recommend that they construe it pragmatically and purposively (rather than literally), using the principle of clinical equipoise and Weijer and Miller’s system of component analysis as a guide to the risk comparisons and risk thresholds that should apply. In practical terms what this means is that Article 5(i) should be interpreted as meaning:

there should be grounds for expecting that administering the medicinal product to be tested will produce a therapeutic benefit to the patient equivalent to standard treatment and outweighing the risks of therapy and produce no serious research risks at all. (Clarificatory words italicised)

Although this entails some stretching of language, we think not to an illegitimate extent. The words of clarification simply ensure that the provision coheres with clinical equipoise and component risk analysis. The Helsinki Declaration endorses clinical equipoise and is referred to in the recitals of the Directive. Clinical equipoise is also a requirement of the Additional Protocol to the Oviedo Convention and not incompatible with the ICH–GCP guidelines, which the Directive meant to give legal weight. Although legal instruments this side of the Atlantic have yet to insist upon component analysis, it was recommended by NBAC and the logic of the argument speaks for itself.

It is important to read the final part of Article 5(i) as if the words ‘no risk’ mean ‘no significant’ or ‘no serious’ risk, because component analysis shifts the risk inquiry to non-therapeutic components of the trial, which will necessarily be associated with some risk. The risk may range from trivial risks of chart review and additional blood sampling (almost an invariable requirement in any drug trial) to (for example) the radiation burden associated with serial X-ray or CT scanning to monitor the efficacy of a novel drug for treating cerebral

should be offered the opportunity to participate in the trial (at least they receive an unproven drug rather than unaffordable therapy), or whether this unreasonably exploits their economic vulnerability.

See above Section II-A.

The CTD refers in particular to the 1996 version which casts doubts on amendments and clarifications made in 2000, 2002 and 2004. But officials have confirmed that the EMEA supports the line taken on placebo trials in the 2000 version of the Declaration: EMEA/CPMP Position Statement on the Use of Placebo in Clinical Trials with regard to the revised Declaration of Helsinki (EMEA/17424/01, 2001); B. van Zweiten-Boot, ‘Choice of Control Groups’ in Academy of Medical Sciences (2003), op.cit., n.3, 79.

See above Section II-A.
haemorrhage. Several of these procedures may be required not only to gather information for the study, but to minimise its risks by allowing early detection and treatment of side effects and complications. Given these considerations, it would be impossible to allocate a description of ‘no risk’ to the non-therapeutic component of most clinical trials.

In our view, the appropriate threshold is that the research components entail no more than ‘minimal risk’. Unfortunately, this does not fit neatly with the current phrasing of the Directive (‘no risk at all’), hence we used the words ‘no serious risk at all’ in the italicised clarification above. That said, we intend it to mean the same thing as minimal risk. If this suggestion were followed, vulnerable individuals unable to give consent would not face undue risks for the sake of society; by the same token, though, this community of people would not be left vulnerable to poor medical care, which could be improved upon by low-risk medical research.

A persuasive case for allowing minimal risk also emerges when one studies international ethical standards. Both the Oviedo Convention and its Additional Protocol recommend the limit be ‘minimal risk and minimal burden’. The ICH–GCP guidance similarly directs that the risks and impact should be low and minimised. NBAC proposed two limits in 2001. It agreed that research should be permitted where it poses no more than minimal risk and further recommended that research posing more than minimal risk should be allowed in exceptional circumstances. The US already adopts the minimal risk position in its Common Rule and allows ‘minor increase over minimal risk’ in paediatric research. NBAC’s proposal to allow more-than-minimal risk under strict scrutiny is supported by the Helsinki Declaration, which does not stipulate a limit to the degree of risk that may be undertaken in research, but instead that research must be justified by its potential value to future care. In practice, this would usually be

116 An ethical case for ‘minimal risk’ is explained below (see Section IV). Weijer also argues that it is consistent with a fiduciary’s duty of care and parens patriae duties: Miller, Weijer (2006), op.cit., n.83; McRae, Weijer (2002), op.cit., n.71, 1149–1150.
118 NBAC (2001), op.cit., n.61, recommendation 2.5. It proposed stricter scrutiny where the research involved risks more than minimal.
119 The US Common Rule (45 CFR 46), which was issued by the DHHS in 1981 and codified in 1991, governs research involving IAs within the category of research with persons ‘vulnerable to coercion or undue influence’. See especially: 45 CFR 46.102(i).
120 Amended Helsinki Declaration Article 28.
equivalent to minimal risk, if the ethical arguments we outline in Section IV were observed. The plain implication is that each of these instruments allows protocols that, overall, add some minimal risk to the patient’s condition, provided it is minimised and proportionate to the scientific knowledge gained. The only disagreement amongst them is whether anything more than minimal should be permitted.

The language used to define minimal risk has tended to vary, but this is not due to substantial disagreement about its merits or scope. NBAC and Weijer support a definition that minimal risk refers to the risks of everyday life in the general (healthy) population. Those who framed the Additional Protocol to the Oviedo Convention deemed that research is considered to involve minimal risk if it is expected ‘to result, at the most, in a very slight and temporary negative impact on the health of the person concerned’ and to involve minimal burden if it is expected that ‘the discomfort will be, at the most, temporary and very slight for the person concerned’. Wendler suggests a twist whereby minimal risk is understood as the level of risk incurred in daily life for charitable activities. All these definitions seem to allow physical and pathophysiological examinations, venipunctures, measurements of central venous pressure when a catheter is in place, questionnaires, review of medical records, additional blood samples and x-rays. It is less clear whether they allow bronchoscopy, spinal taps or cardiac puncture. Lumbar punctures and PET scans are generally viewed as having greater-than-minimal risk because complications can require surgery to correct.

122 Once, that is, it is understood that minimal risk applies to the risks of research and not therapeutic components of the trial. A residual criticism is that the standard is too vague: NBAC (1998), op.cit., n.61, chapter 4 citing Loretta Kopelman.
123 NBAC (2001), op.cit., n.61, recommendation 4.2; NBAC (1998), op.cit., n.61, chapter 4. McRae, Weijer (2002), op.cit., n.71, 1150. NBAC suggests that the general population be used as a benchmark because the risks faced in their daily lives are usually lower than those confronted by patients. NBAC added a caveat that if the study nonetheless poses higher risk for any prospective participants then the ethics committee should insist on additional safeguards.
124 Additional Protocol to the Oviedo Convention Article 17.
126 Further discussion is needed about the importance of these procedures in research with IAs. Perhaps the European legal framework should allow research risks slightly above minimal provided such research is subject to more rigorous scrutiny. Further discussion of the ethical legitimacy of such a framework would be required.
In conjunction with these proposals, we also recommend that the EC and Member States support ethical and legal research to develop guidelines for complex risk comparisons. For example, in severe traumatic brain injury, is death a more serious risk for a patient than staying alive in a persistent vegetative state or with minimal consciousness? Or in stroke research is one to regard having aphasia as more harmful than a paralysed arm? While the subjectivity and incommensurability of risk is not caused by the Directive, it is an issue that must nevertheless be tackled by Member States when implementing governance frameworks. Component analysis helps ameliorate the difficulties for ethics committees and competent authorities. The non-therapeutic components can, in most circumstances, be assessed straightforwardly by an ethics committee. The risks associated with therapeutic components of the protocol need not be measured precisely. The two questions are: (a) does the medical profession have a bona fide belief that the net balance of risks and expected benefits in each trial arm are equivalent, meaning the research subjects will not be denied clinical care at least as good as standard treatment? and (b) are the therapeutic risks balanced by the expected therapeutic benefits as they would be in clinical practice?

B. Permitted Investigations

Notwithstanding sensible risk thresholds, further protections are needed to protect IAs from unfair studies. For example, unscrupulous researchers might seek to enrol IAs in research projects because they find them more compliant, easier to enrol (e.g. their representatives might be untroubled by risk)\(^\text{127}\) or more convenient (e.g. they already have a central venous catheter in place).\(^\text{128}\) A common way to implement this ethical consideration is to insist that the investigators evidence the importance of the research (e.g. the problem it addresses; its statistical power) and that it cannot be performed as effectively using legally competent persons.\(^\text{129}\) For example, research on plastic surgery, infertility treatment or setting fractures should not involve IAs because this research can be carried out as effectively with competent adults. Some legal instruments also require proof that the research will benefit ‘a community of persons to which the research participants belongs’ or ‘persons having the same condition’.\(^\text{130}\) This is a superfluous flourish

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\(^\text{128}\) Karlawish and Hall, op.cit., n.121, 502.

\(^\text{129}\) E.g. Amended Helsinki Declaration Article 24.

\(^\text{130}\) Ibid.
(since it could legitimately be said that IAs belong to the community of IAs or have the condition of ‘incapacity’), but generally unproblematic.\footnote{It is generally unproblematic to read it more narrowly—for example that persons suffering from a stroke must not be involved in research unless it relates to treatments for stroke (or knowledge about strokes)—because physicians rarely want to involve IAs in other research. However, situations can be envisaged which demonstrate that the condition is not helpful. For example, a physician-researcher might propose a large-scale study to investigate the impact of socio-economic factors on the quality of proxy decision-making. He might propose to enrol a wide variety of IAs—some suffering stroke, cardiac arrest, sepsis, etc. The issue here is not to ensure that the patient-subjects suffer from the same condition, but that they have not been chosen because they are easy to exploit. There should be an independent, demonstrably valid reason for including them.}

Article 5(e) of the Directive reformulates and attempts to improve upon these conditions. It states that research is prohibited unless it is essential to validate data [already] obtained in clinical trials on persons able to give informed consent or by other research methods.

The unusual phrasing is helpful because it prevents research until appropriate preparatory studies with animals and other adults have been completed. This issue is not explicitly observed by the Helsinki Declaration although ethics committees usually require it.\footnote{For a controversial study where insufficient preliminary studies were conducted: Huang \texttt{http://www.hinduonnet.com/fline/81824/18241140.htm}; \texttt{http://www.hsph.harvard.edu/bioethics/archives/200108/msg00008.html}}

An additional clause in Article 5(e) was however ill-advised. It states that research is prohibited unless it relates directly to a life-threatening or debilitating clinical condition from which the incapacitated adult suffers[.]

The intention, it seems, was to ensure that IAs are not involved unless the research benefits people like them. The phrasing would have been better if it had simply used the familiar wording that research involving IAs is prohibited if it can be performed as effectively on competent persons.\footnote{See e.g. Helsinki Declaration Article 24; ICH–GCP 4.8.14; Oviedo Convention Article 17(1)(ii); Additional Protocol Article 15(1)(ii); Mental Capacity Act 2005 s.31.} Unfortunately, the wording adopted in the CTD leads to confusion. Interpreted narrowly it prohibits research into the general care of IAs that falls short of direct clinical treatment. A relevant example is research into the rate or volume of ventilatory support in those being treated during or after cardiac arrest, the importance of which was highlighted in recent observational and experimental
studies.\textsuperscript{134} Such research would not relate \textit{directly} to a clinical condition (\textit{i.e.} cardiac arrest) but rather to supportive therapy and, therefore, would be unacceptable according to a strict reading of Article 5(e).

A further confusion to which this language may lead is an insistence that research relate to a condition which is \textit{caused} by mental incapacity. This is not what was intended and, to our knowledge, Member States have thus far avoided this reading. However, confusion arose in England during the passage of the Mental Capacity Act 2005,\textsuperscript{135} and it is important that similar mistakes are not made by ethics committees. Some debilitating clinical conditions result in mental incapacity as a consequence of non-neurological disease or essential therapy. For example, patients with serious infections often develop severe respiratory failure. In such patients, the severe systemic illness affects capacity, rather than the other way round. Thus, policies requiring the mental incapacity to be a cause of the condition studied would be unworkable.

Another example arises when patients have artificial ventilation delivered through a tube in the windpipe. This is usually very uncomfortable and patients are given strong painkillers and sedatives to make them more comfortable. The condition studied arises independently of the incapacity, so a policy insisting on a causal relation would be problematic.

Care must also be taken to avoid reading Article 5(e) in a way that prevents research that seeks to study possible complications of incapacitating disease. Airway reflexes are compromised in patients with a depressed level of consciousness, resulting in an increase in the incidence of aspiration pneumonia. Research aimed at preventing such pneumonia is clearly in the public interest and can only be studied effectively with the involvement of incapacitated patients, some of whom may not have developed pneumonia. A policy that insists that the patient belong to a community of persons suffering the condition would be problematic.

\textbf{C. Proxy Consent}

One of the most familiar legal and ethical standards for research with IAs is the requirement to seek consent for research from a person acting as the representative of the IA. The CTD reflects this in Article 5(a). It poses three problems. Most significantly, the Directive fails to recognise any exceptions to the requirement for prior consent, which has caused severe problems for research into emergency and critical


care in some Member States, including England. We examine this issue below. A second problem is that those drafting the Directive shied away from defining who should be recognised as the legal representative of an IA. As a result, Member States have defined the people that can act as a ‘legal representative’ in highly disparate ways. A comparison is provided by Lemaire et al.136 In Austria, Germany and the Czech Republic, the representative must be appointed by a judge. In the Netherlands, a spouse or life companion may act as proxy. England, Wales and Northern Ireland have adopted a much broader and highly unusual policy. They allow any person who ‘by virtue of their relationship’ with the IA is ‘suitable’ and ‘available and willing’ to act as the legal representative. In addition, if there is no such person, a doctor primarily responsible for the patient’s medical treatment or a person nominated by their doctor or the NHS (if applicable) may act. The important caveat is that the doctor or NHS nominee must not be connected with the conduct of the trial. This means they must not be an investigator, a sponsor, a person engaged by, or acting in concert with, the sponsor or trial manager or under the direction or control of the sponsor, investigator or collaborator.

The CTD encourages the variety of definitions by explicitly stating that the concept of ‘legal representative’ is to be determined by national law (Recital 5). Although some pluralism is justified, it presents three sets of problems. In the first place, the various definitions impact on international trials making them cumbersome and unwieldy. Second, researchers in countries with a narrow interpretation of ‘legal representatives’ report extensive difficulties. In the main, it is simply not feasible for researchers to instigate legal proceedings before commencing research. This is relevant not only to emergency research (discussed below) but also to research on diseases such as dementia and stroke. Third, it allows Members States to define legal representatives in an unethically broad way, irrespective of whether the representatives are appropriately qualified or subject to potential conflicts of interest. Recent experience in the US (after US federal regulations left the definition to individual States) suggests these issues could be quite divisive.137

In our view, the CTD missed an important opportunity to achieve greater harmonisation and an appropriate definition of legal representative. It ought to have focused on the purpose of seeking proxy-consent and defined legal representatives as including a current partner, close

136 Lemaire et al. (2005), op.cit., n.13.
friend, relative or carer, or other person who is properly acquainted with the individual\textsuperscript{138} and expects to have contact with the individual during the course of the research.\textsuperscript{139} The rationale behind proxy-consent is to imitate the checks and balances normally provided by the subject, which the IAs cannot do for themselves because they lack the requisite capacity. Following the Kantian ideal described below, the proxy should give some thought to principled autonomy, including obligations to reason rationally and not ignore the importance of research for other vulnerable IAs.\textsuperscript{140} They should also prompt some consideration of this \textit{particular patient’s} risk situation, which ethics committees are not in a position to consider (e.g. does the individual have a low pain threshold, a longer distance to travel, a fear of needles?). The proxy should be present for the duration of the research, ready to revoke consent if the burdens become too great (in the same way that a competent adult might remove themselves from a trial). That said, the proxy should be regarded as holding a power of veto rather than being the primary risk assessor. That responsibility (including possible legal liability) must rest with medical professionals (and to some extent ethics committees) who have the skills and experience to monitor and assess the patient’s clinical condition, clinical equipoise and research risks.

If there had been some serious deliberation about the role of proxy-consent, consensus might have been possible in the CTD. We recognise that it is now unlikely that Member State governments will tackle this task. The most practical course is thus to encourage countries with narrow definitions to appreciate the value of a definition of legal representative that does not require court involvement. Furthermore, countries following the English definition should allow doctors to give proxy-consent only in exceptional circumstances. Harmonisation might in this way be indirectly achieved.

A third problem stemming from Article 5(a) concerns the revocation of consent. Article 5(a) states that consent to enrol an IA in a clinical trial may be revoked at any time. In some senses this is clear and provides important safeguards. The proxy may order researchers to cease administering a test drug or placebo. They may also prospectively decide that no additional tissue or data be collected. What is less clear

\textsuperscript{138} A personal representative is more likely to know whether the IA has special idiosyncrasies that are likely to affect the way they experience the research. For example, the magnitude of pain and anxiety may be much greater in an intellectually disabled person with a fear of needles than a 30-year-old diabetic. They may know that the IA has a duodenal ulcer, meaning an aspirin may (unusually) present more than minimal risk: Karlawish and Hall, \textit{op.cit.}, n.121, 502.

\textsuperscript{139} NBAC (1998), \textit{op.cit.}, n.61, text to recommendation 14.

\textsuperscript{140} See below Section IV-D.
is whether the legal representative has the power to order that the tissue and data collected up to that point be destroyed or not be used for research. For example, might the legal representative order that data about the patient recorded in tables and databases be erased or blocked? A power of this kind could create practical difficulties for researchers. Some have also argued that it would introduce serious bias in research with critically ill patients on the assumption that survivors will be more likely than non-survivors to order the destruction of data.\textsuperscript{141} This would undermine the effect of randomisation.\textsuperscript{142} The counter-argument is that researchers should respect the participants’ privacy. Our own view is that the matter should be governed by the Data Protection Directive 95/46/EC and the European Convention on Human Rights (‘ECHR’), not by arbitrary determinations under the CTD. Directive 98/44/EC and the ECHR uphold the right to a private life, but allow interferences in privacy that are necessary for the protection of health and proportionate to the protection of health.\textsuperscript{143} Directive 98/44/EC also provides that data legitimately collected for clinical purposes may be processed for compatible purposes, and further processing of data for historical, statistical or scientific purposes shall not be considered incompatible provided that Member States provide appropriate safeguards.\textsuperscript{144} On the strength of these arguments, it might sometimes be said that the privacy interests of research participants are not illegitimately interfered with when data collected \textit{up to the point of withdrawal} is used after withdrawal. However, such arguments will be less persuasive where the requirements for proxy-consent have been waived or deferred (see Section III-D), the data is sensitive, the analysis is likely to cause harm or substantial distress, it is possible to separate the data collected before withdrawal and the risk of bias is small.

\textbf{D. Research without Proxy Consent (\textit{e.g.} in Emergency Situations)}

As mentioned, one of the most serious problems with Article 5(a) is its exceptionless nature. It requires written consent to be given by a legal representative on every occasion prior to involving an IA in a clinical

\textsuperscript{141} MHRA, \textit{Draft Guidance on Consent by a Legal Representative on Behalf of a Person not Able to Consent Under the Medicines for Human Use (Clinical Trials) Regulations 2003} (2003) para 76; see the solution proposed: \textit{Ibid.}, para 77.


\textsuperscript{143} Directive 95/46/EC Article 8(3), Recital 34. Also Articles 10, 11 (read in light of Recitals 38, 39).

\textsuperscript{144} See, for example, Directive 95/46/EC Recital 45 and Data Protection Act 1998 (UK) s.10, 33(2).
This creates serious problems for emergency and critical illness research that address some of the most devastating conditions, including cardiac arrest, strokes, head injuries, arrhythmias and shock. Typically, treatment for these conditions must commence within hours, preferably as soon as possible. For example, the best available data show that every minute of delay in providing treatment for cardiac arrest reduces the chance of success by over 20% compared with that in the previous minute. Where it is proposed that research should be linked to treatment, it must also commence swiftly or not at all. Most studies use a time window of 8 hours, some a window of 4 hours and some allow inclusion up to 12 or 24 hours after injury. It is often impossible to seek consent within this narrow time frame because the patient is unconscious and unaccompanied. In other situations, it may be possible to contact the proxy but the time taken delays treatment. For example, the authors of the National Acute Brain Injury Study (Hypothermia) reported that processes to obtain witness-signed proxy-consent resulted in low accrual to the research trial and, because it delayed therapy by approximately 45 minutes, in late achievement of the target temperature that might have improved patient outcomes.

One counter response is that research of this kind is ethically unsound and should simply not take place. After all, little information may be available about the IA’s preferences or medical history—even the person’s identity may be unknown. Such an attitude seems to protect patients, but it is highly inadvisable because it would inhibit research into almost all aspects of cardiopulmonary resuscitation and most aspects of intensive care medicine. As Section I made clear, such research ought to be regarded as a public health priority. Just one example of the sort of research that is impossible if consent is insisted

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145 Oral consent in the presence of a witness is permitted if the individual is ‘unable to write’: CTD Article 3(2)(d). It is ambiguous whether a physician-researcher may proceed with research if he has managed only to contact an able-bodied, literate legal representative by telephone. The intention was probably to allow this if another witness is present.


147 Kompanje et al., (2005), op.cit., n.24.


149 Kompanje et al., (2005), op.cit., n.24.


upon was the Hypothermia after Cardiac Arrest Study. The study demonstrated that it is better to use mild hypothermia (2 degrees) after resuscitation than the stronger degree of cooling that doctors had been using for years.\textsuperscript{152}

The insistence on consent in the Directive is as surprising as it is problematic. The ICH–GCP guidelines, which had a strong influence on the text of the CTD, permit this type of research.\textsuperscript{153} Since 2000, the Helsinki Declaration has also permitted emergency research without prior consent, if it is not possible to seek proxy or advance consent, and the physical/mental condition that prevents obtaining consent is a necessary characteristic of the research population.\textsuperscript{154} Like the ICH–GCP, the Declaration states that consent to remain in the research should be obtained as soon as possible from the individual (when they recover capacity) or a legally authorized surrogate. Similar conditions are set by the Additional Protocol to the Oviedo Convention. It also states that the research should entail no more than minimal risk and should not deprive the subject of medically necessary clinical procedures.\textsuperscript{155} The failure of the Directive to provide leeway for emergency research is even more strange in light of the experiences in the United States. Policymakers in that country developed several different models (albeit with some imperfections) in the 1980s and 90s to permit emergency research. Moreover, the problems of overprotection became clear during the three-year moratorium on emergency research in the mid-1990s.\textsuperscript{156}

The early US model for emergency research included provisions in Department of Health and Human Services (DHHS) regulations through which consent could be waived if necessary, the research posed no more than minimal risk, the waiver did not adversely affect the participant’s rights and the participant would be provided with additional information after participation. This was a sensible system, but unfortunately misinterpreted by investigators, Institutional Review Boards and federal regulators. Instead of assessing whether research components could be described as minimal, many applied the minimal risk standard to aggregate risks (including clinical risks). Given the seriousness of the ICU patient’s underlying condition,\textsuperscript{157}

\begin{footnotesize}
\begin{enumerate}
\item[\textsuperscript{152}] Cardiac Arrest Study Group, \textit{op.cit.}, n.28.
\item[\textsuperscript{153}] Paras 3.1.7 and 4.8.15.
\item[\textsuperscript{154}] Amended Helsinki Declaration Article 26.
\item[\textsuperscript{155}] Additional Protocol to the Oviedo Convention Article 19.
\item[\textsuperscript{157}] McRae, Weijer (2002), \textit{op.cit.}, n.71, 1146–1150.
\end{enumerate}
\end{footnotesize}
this led them to think consent could not be waived in intensive care or emergency protocols. To side-step this problem, researchers and IRBs developed a second model for approving these protocols. This was known as ‘deferred consent’. It involved seeking consent from the patient-subject or proxy consent for the protocol within 48 hours. However, the Office of Protection for Research Risks (OPRR) declared the ‘deferred consent’ mechanism to be untenable\(^\text{158}\) because, it argued, it is not possible to agree to, or to refuse, a procedure that has already been performed. At this point, emergency research ground to a halt.

Over the next three years, investigators and the DHHS (including the OPRR and the FDA) worked on a third regulatory model that eventually replaced the old regulations\(^\text{159}\). The new regulations, which have been operating since 1996, include the usual conditions that consent not be feasible, that the research hold the prospect of benefit and that the research not be possible without the waiver. However, further requirements were added that have since led to difficulties. For instance, the research must relate to a life-threatening condition. This makes it very difficult to research some non-life-threatening conditions for which treatment and research must also commence as a matter of urgency. An example might be research into rapid pain relief for renal colic. Another limit is that research can take place only if no satisfactory treatment is available. This has proved difficult to interpret in trials of artificial blood. It is widely agreed that PolyHeme trials should go ahead in out-of-hospital situations (saline is not a satisfactory treatment) but, in the case of in-hospital trials, there is much debate whether donor blood transfusions (which have several attendant problems) constitute satisfactory treatment\(^\text{160}\). The new regulations also require public disclosure of the study and its results, and community consultation. Although meant to increase transparency and accountability, these conditions have proven cumbersome, unclear and of no particular benefit\(^\text{161}\). A further problem is that the minimal risk threshold was substituted with the requirement that risks be ‘reasonable in relation to what is known about the medical condition of the potential class of participants, the risks and benefits of standard therapy, if any, and what is known about the risks and benefits of the proposed intervention’.

\(^{158}\) Ibid. 1146–1147.


\(^{161}\) MHRA, \textit{op.cit.}, n.141, para 53.
In effect, this change precludes component risk analysis and exposes patient-subjects to the problems associated with aggregate risk analysis.\(^{162}\)

The failure of the CTD to address emergency research has left European Member States in a quandary. To avoid the problems of a moratorium, but in the absence of clear guidance, their response has been diverse, which in itself is problematic because one of the primary purposes of the CTD was to increase harmonisation.\(^{163}\)

An unusual solution was implemented in England, Wales and Northern Ireland. As noted above, these countries defined the term ‘legal representative’ very broadly, which means that a health professional with no connection with the research [including a hospital doctor, chaplain, ambulance officer or clinical ethicist (amongst others)] can be appointed as the patient’s legal representative if a personal representative cannot be contacted in time. Two problems arise. The first is that once the professional consents, there is no legal requirement to inform a close friend, relative or carer as soon as reasonably practicable, nor to have them take over the role of representative.\(^{164}\) The professional’s approval is regarded as a valid form of proxy consent even where they have no on-going contact or personal acquaintance with the patient. Second, the broad definition is not a complete solution because it can still be difficult to find a person unconnected with research within a very short therapeutic window. For example, the TROICA trial administered a thrombolytic test-drug or placebo to patient-subjects who were not resuscitated immediately after a heart attack.\(^{165}\) To be of any use, it was necessary in out-of-hospital situations for the attending paramedic to administer the test-drug which meant that, technically, the paramedic was ineligible to act as the patient’s legal representative because he was considered to be ‘connected with the trial’. No other person was available to give consent. Although the study was approved by UK ethics committees, the UK trial sites could not go ahead. A further difficulty is that ambulance officers may be eligible to act as the legal representative but unwilling to accept the

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162 See above Section II-A.


164 The draft guidance is equivocal: MHRA, op.cit., n.141, para 47 (‘may’); c.f. paras 65, 75.

165 It was thought that the test-drug might help break down the blood clots that begin to form during the infarction. These clots block the small blood vessels limiting recovery when resuscitation eventually takes place: F. Spohr et al., ‘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’ (2003) 35 European Journal of Clinical Investigation 315–323.
responsibility. This is particularly problematic in the UK where ambulance officers attend incidents without a doctor. 166

In contrast, the TROICA trial went ahead in other Member States including Austria, Belgium, France, Germany, the Netherlands, Norway and Spain. These countries have established a system similar to the old US federal regulations. They waive the requirement for proxy consent if treatment and associated research must commence as a matter of urgency. The survey by Lemaire et al. indicates that they defer the requirement for consent, rather than allowing a complete waiver. 167 As with the Helsinki Declaration and the Additional Protocol, the individual or their representative must be informed of the research and their consent obtained for continued participation. Set up properly, this procedure does not actually rest on the concept rejected by the OPRR that consent can be obtained ex post facto. Instead it legitimises the decision to enrol without consent by insisting that researchers be transparent about what has been done, and that they seek consent to continue the research as soon as the emergency passes. As a further safeguard, the period of time during which consent is waived can be capped. In Austria, consent may be deferred for as long as the emergency lasts. 168 In the Netherlands, the phrase is ‘so long as the circumstances which make it impossible for consent to be obtained continue to prevail’. 169 Austrian law also requires that a notice be posted at the site of the clinical trial to notify the public that clinical trials are being conducted on patients who are not able to consent. 170

Member States were bold to press ahead with laws allowing consent to be waived notwithstanding the apparent limits of Article 5(a) of the Directive. 171 The UK government initially considered this approach, but received legal advice to the effect that it would not comply with the CTD. The government also contemplated a system under which emergency research might be approved in advance by an ethics committee. The argument in favour was that the CTD allows legal persons as well as natural persons to act as a legal representative. 173 However, it seems the government lawyers advised that for consent by a

166 A straw poll of paramedics who might have been involved in TROICA trial confirmed this issue. The situation in continental Europe differs since a doctor will usually be sent out with the ambulance.


168 § 43a Arzneimittelgesetz.

169 The Medical Research Involving Human Subjects Act s.6(2)

170 A poster at the department, or a posting on the website is considered sufficient.

171 Lemaire et al. (2005), op.cit., n.13.

172 In relation to UK, Wales and Northern Ireland (not Scotland).

173 CTD Recital 5.
‘representative’ to be valid, they needed to consider the subjective circumstances of the individual patient. Ethics committees considering research in advance could not do this. For this reason, the UK government concluded that it had implemented the CTD as generously as possible. The problems highlighted by the TROICA trial led it to review its regulations within 18 months. It is likely the amended regulations will allow consent to be waived in situations where clinical treatment must commence as a matter of urgency and it is necessary to take action for the purposes of a trial. The initial proposal was that the waiver period should be capped at 24 hours, although organisations representing medical researchers responded that this may prove too short. The final version is yet to be laid before Parliament.

Despite obvious opportunities to object, regulatory bodies in Brussels raised no complaint about the mismatch between laws that waive consent and Article 5(a). France, Belgium and the Netherlands openly chose to maintain the systems of waiver that operated in their countries before 2004, and the UK publicly raised the issue in its consultation process. It seems a view is forming that the European legislative bodies never intended to block emergency research, and thus the text of Article 5(a) need not be adhered to literally. The Commission appears to agree. It states in Recital 10 of Directive 2005/28 (the Good Clinical Practice Directive):

The detailed rules adopted in Member States pursuant to Article 3(1) of Directive 2001/20/EC to protect from abuse individuals who are incapable of giving their informed consent should also cover individuals temporarily incapable of giving their informed consent, as in emergency situations.

The flexibility of European authorities on this issue is significant. They realise that certain issues were not given the detailed consideration they deserved and that Member States should be allowed some latitude in their implementation of the CTD. This bolsters our arguments for a strongly purposive interpretation of Article 5(i) in Section III-A.

In most jurisdictions, laws on deferred consent are currently limited to emergency situations, or situations where it is not possible to contact a

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174 See MHRA, Consultation on Amendment to the Medicines for Human Use (Clinical Trials) Regulations 2004 (SI 2004/1031) MLX 326 (ended October 2005). It is planned that the revisions will also be implemented in Scotland.

175 Medical Research Council, Response to Consultation on the Amendment to the Medicines for Human Use (Clinical Trials) Regulations 2004. Some have suggested that 48 hours is the minimum practical time.

176 The proposal was delayed first by the political climate following the TGN1214 clinical trial disaster, and then again for unspecified reasons.
legal representative. Some commentators have argued that they should be extended beyond this. In some situations, most notably critical illness, it may be possible to contact the legal representative, but the pressure of the clinical situation makes the process of proxy-consent for medical research highly strained. Confronted with the complexity and stress of critical, terminal or end-of-life illness, relatives and friends often struggle to weigh the evidence for and against research. They lack the time or composure to grasp the principles underlying clinical equipoise and minimal risk. As a result, many mistakenly think the research is likely to help the IA or that the research is substantially riskier than normal procedures. Others misjudge the preferences of the IA\textsuperscript{177} and many decline to make a decision, which in effect counts as a refusal.

If deferred consent is extended, it is important to avoid undue paternalism. England, Wales and Northern Ireland are experimenting with such an approach. The broad definition of legal representatives adopted in these countries allow the patient’s doctor or another person appointed by the health service (provided they are not connected with the conduct of the trial) to assume the mantle of the patient’s representative when a more suitable person is not willing to act. The advantage of this approach is that family members can opt to have someone else make the decision, but their prerogative remains intact. In this model, it should be clear that a more personal representative always retains power to break off the trial, even if a professional representative gave the initial consent for research. The professional representative should also be responsible for monitoring the IA’s well being for the duration of the research. This approach is consistent with the CTD, Helsinki Declaration and Oviedo Convention because none limit the definition of ‘legal representative’.

\textbf{E. Ethics Committee Review}

A final issue to consider is the form and role of ethics committees under the CTD.\textsuperscript{178} It stipulates that Member States must establish independent, expert committees to review protocols within a statutory period and lists several issues to be considered. It is mandatory not

\textsuperscript{177} Kompanje \textit{et al.} (2005), \textit{op.cit.}, n.24; Mason \textit{et al.}, \textit{op.cit.}, n.127, 61–62.

only to obtain a favourable opinion before a clinical trial is commenced,\textsuperscript{179} but also to notify the ethics committee when the clinical trial has ended and if ‘substantial’ and ‘significant’ amendments are made to the protocol. In this way, the CTD adds a legal footing to ethic committees’ authority and takes steps to address the infamous heterogeneity, inefficiencies and lack of on-going monitoring.

These are welcome developments; however, there is some doubt whether the CTD will improve efficiency. Although an ethics committee must give its decision within a strict 60-day period,\textsuperscript{180} the clock starts running when the ethics committee acknowledges receipt of a completed application and it is unclear what action researchers or subjects can take if delays arise. At one point, it was proposed that certain types of studies might commence in advance of the decision being made. This was dropped from the final text. Furthermore, although Article 7 states that Member States should arrange for the adoption of a single opinion, some Member States including the UK have implemented hybrid systems with central regional committees and influential local ethics committees. In one sense, the CTD is complied with because a single opinion is rendered by the lead committee, but the process it remains open to delay, duplicated deliberations, inconsistency and unpredictability. Local review helps to consider the burdens on particular populations, most notably hospital staff and local ethnic populations,\textsuperscript{181} but it is advisable to limit the remit of local committees and the time they are given for deliberation.\textsuperscript{182}

There is also some uncertainty about provisions directed more specifically at the ethical review of trials involving IAs. For example, the CTD prohibits such trials if they offer incentives or financial inducements beyond ‘compensation’, but offers no pointers on how to distinguish these payments nor the levels of compensation that are

\textsuperscript{179} CTD Article 9(1). Responsibility for seeking an opinion rests with the sponsor.

\textsuperscript{180} A single suspension of time is allowed if the REC seeks additional information from the applicant. No extensions are permitted except a 30-day period where the trial involves certain kinds of genetic technology.


\textsuperscript{182} For example, one multinational research project, which proposed to survey the opinions of patients and their relatives on the ideal qualities of an intensive care doctor, was approved by ethics committees in eight Member States, but rejected twice by an UK multicentre research ethics committee (MREC) before being approved on appeal by a second MREC. However, the second MREC still required the local study coordinators to obtain approval from their local research ethics committees (LRECS) in each of ten participating hospitals: relevant papers and correspondence with authors.
appropriate. Article 5(g) further directs that ethics committees should not make a decision on a trial involving IAs unless they have expertise in the relevant disease and the patient population or they take advice in the ‘clinical, ethical, psychosocial questions in the field of the relevant disease and patient population’. Member States are implementing this in different ways because it does not indicate the number of people who should be consulted nor how to define the patient population. A further complexity is the lack of resources, particularly in new Member states and those preparing for accession (e.g. Croatia). Few ethics committees (even in large Member States) have members with the necessary expertise. Accordingly, they must find sufficient funds to commission specialist reports and factor this into the 60-day response time. Consideration might need to be given to special training programmes or a special office, either at national or European level, to lead and coordinate the oversight of trials involving IAs. A special panel of this kind exists in the US for paediatric research involving more-than-minimal risk.

IV. ETHICAL JUSTIFICATIONS

The critique we have presented of Article 5 of the CTD criticises it for both permitting, and prohibiting, too much. Our emphasis has been on showing the importance of involving IAs in research that will not benefit the individual participants. It is useful therefore to say a few words about the normative anchor that grounds our recommendations.

A. Utilitarian Justification

The utilitarian credentials of a pro-research position are fairly plain. Involving IAs in research produces the maximal balance of positive value over disvalue for all those affected. The knowledge we learn from exposing a few IAs to the risks of untested drugs and procedures will help prevent deaths and suffering in a much larger number of IAs who suffer from the same condition or disease in the future. There is no other way to ensure reliable therapies and high-quality care for the problems of Alzheimer’s Disease, stroke, heart attack and psychiatric

\[183\) CTD Articles 5(d); 6(3)(j).
\[184\) NBAC recommended two in its 1998 report: NBAC (1998), op.cit., n.61, Executive Summary.
\[185\) For example, this might be a responsibility for the MHRA.
\[186\) One of NBAC’s specific recommendations was that a Special Standing Panel (SSP) should be established to review protocols referred by IRBs for research involving IAs: NBAC (1998), op.cit., n.61.
\[187\) Utilitarians, typically define positive value as happiness, health, well being or preferences.
illness, to mention just a few conditions. The utilitarian argument does not, however, advocate unconditioned research. The felicific calculus gives weight to the importance of being able to trust that doctors will not seriously harm their patients, that individuals will not be unfairly singled out for research and that patients’ individuality and dignity will be respected. This sort of reasoning has many supporters, but also many detractors. Although logical at one level—few would argue with the idea that we should maximise positive value and minimise evil—the utilitarian’s *overriding* concern with maximising good consequences for everybody *unreliably* protects an individual’s right to respect, dignity and integrity. Under a utilitarian framework, these matters may be traded off if it will produce more utility. Furthermore, the utilitarian rarely has concrete proof that the particular constraints he supports do in fact maximise utility. It is difficult to set aside arguments that stronger or more lax conditioning of research would be better. For these sorts of reasons, policy propositions that rely purely on utilitarian reasoning tend to be viewed with suspicion.

This is precisely the undercurrent in much legal scholarship. Commentators believe that arguments for research involving IAs, particularly arguments that recommend non-therapeutic research, are based upon utilitarian reasoning and that the conclusion we should draw about such arguments depends on one’s view about utilitarianism. If we take the flaws in utilitarian reasoning seriously, we should reject pro-research arguments. At times, this point is made explicit. For example, in a detailed and informative article, Lewis writes:

> There is a choice to be made between the utilitarian and deontological approaches. Habitually, we avoid this choice by finding some method of allowing these procedures [so-called non-therapeutic research] while still maintaining the pretence of respecting the personhood and dignity of the incompetent ... In the context of non-therapeutic research, [international ‘consensus’ provides] a justification for a utilitarian calculation that allows the use of vulnerable members of society in order to benefit others. Hiding the choice does not make it go away.188

We disagree. In our view, there are several lines of reasoning that justify research involving IAs without invoking utilitarianism. This means there are good reasons for society to regard research involving IAs as ethical even if it doubts the merits of utilitarianism. If this point were more widely recognised, policies and public debates about research with IAs

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188 Lewis, *op.cit.*, n.18, 616–617.
would be more coherent and proposals to facilitate research more respected.

**B. Political Consensus**

Lewis alludes to one line of reasoning in the quotation above. She says, in a critical tone, that international consensus has given the utilitarian calculus legitimacy it does not deserve. In our view, the idea of political consensus should not be swiftly dismissed as empty rhetoric. Elsewhere, one of us (KL) has explained this in greater depth,189 drawing on John Rawls’ later work.190 Broadly speaking, it is argued that political consensus is a sensible way to establish, and to assess, the fairness and legitimacy of a legal policy given the extensive moral pluralism that characterises debates about bio law. Moral theories help us understand the pluralism, but rather than resolve it, they demonstrate that the pluralism is reasonable and therefore likely to be enduring. In light of this, it is preferable, for the sake of social stability, to introduce laws that reflect an ‘overlapping consensus’ of reasonable moral beliefs rather than assert that one particular moral viewpoint is true and others false.191

It is important to recognise that the Rawlsian ideal recommends a very particular type of consensus. It denigrates false consensus that owes more to: *a modus vivendi* based on interest-based bargaining; consensus principles that are no more than aspirational, motherhood statements; or consensus which conceals an orchestrated effort to disenfranchise certain viewpoints.192 In contrast, overlapping consensus is built upon morally cooperative deliberation that gives all those affected genuine reason to think that their moral viewpoints have been understood, valued and respected. We lack the detailed empirical data to know whether Lewis is right to think that the international agreements (for example, the Helsinki Declaration) that support

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191 In Rawls’ idea of public reason, reasonable citizens strive to find legal standards that all citizens can mutually agree to accept and regard as compatible with their comprehensive moral beliefs, in view of the fact that they live in a free but consequently radically pluralist society. Rawls’ normative imperative is based on citizens’ desire to promote their moral powers and freedoms while recognising that moral neutrality is not immediately possible. Instead, they seek laws that reflect fair terms of cooperation: Liddell, *op.cit.*, n.190, 171.
192 These forms of consensus are indifferent to the normative authority of morality and precipitate instability as groups clammer to assert their beliefs whenever they have the power to do so.
research with IAs are merely a front for utilitarianism, or whether the deliberations were aimed at a moral overlap. However, the extensive conditions and constraints decided upon in the Helsinki Declaration seem to us to suggest the latter. The result is that research is permitted, indeed encouraged, in order to reduce future suffering, provided, amongst other matters, it is scientifically astute, necessary, the individual is not seriously harmed, the individual is given best proven therapies, there is minimal interference in their decisional freedom and trustworthy mechanisms of oversight are established. Examined in the abstract, these rules may seem incompletely theorised and to comport with no particular ethical theory, suggesting they have no normative authority (a criticism made by McLean and Ellison). But seen through the lens of Rawls’ ideal of overlapping consensus, the fairness and legitimacy of the rules is clear and apparent. The rules emphasise the commonalities amongst the full range of ethical views and minimise their differences, thereby producing a framework that all citizens could concede is reasonable once they acknowledge the fact of reasonable pluralism.

C. Ethical Principlism

A second line of reasoning rests on ethical principlism which, in turn, is based on arguments about moral convergence and common morality. Brief renditions are common, but for a more detailed explanation why this ethical framework supports research with IAs, we recommend the account by Ackerman. Similar to the Belmont Principles, he argues that moral beings have three relevant interests: exercising autonomous choice, securing fair treatment, and protecting and promoting high standards of personal welfare. These interests generate obligations owed by other individuals, including doctors and putative research subjects.

An individual’s interest in the exercise of autonomy is reflected in obligations of interpersonal conduct, including obligations to respect the capacity of persons to deliberate about, and act on, their life plans and to support them to do so. In the research setting, this is generally given more specific recognition in duties to secure informed

193 Amended Helsinki Declaration Article 32.
196 See e.g. the succinct account by Silverman et al., op.cit., n.101, 1724–1726.
consent and to respect the privacy of persons and the confidentiality of data.\textsuperscript{198}

The individual’s interest in fair treatment generates an obligation to distribute the benefits and burdens of cooperative social endeavours so that each person has an equal opportunity to pursue their life plans.\textsuperscript{199} In the research setting, this obligation means that subjects should be selected in ways that do not impose arbitrary or heavy burdens on specific classes of persons, that subjects with special vulnerabilities should be more strongly protected than less vulnerable subjects and that the benefits of research should be fairly allocated.

Finally, the individual’s interest in having high standards of personal welfare protected and promoted generates obligations of beneficence. In the context of research, this means doctors (and society more generally) have a duty to avoid designing trials that would deprive individuals of reasonable standards of medical care, to assess the safety and efficacy of standard medical procedures whose value is uncertain, to minimise risk and to avoid exposing any person to serious risks not intended for their benefit.\textsuperscript{200} An obligation also exists, Ackermann argues, to provide and enhance the essential conditions its members need to pursue their life plans including adequate housing, nutrition, education and medical care. Since medical research is the powerhouse of evidence-based medicine, it is an essential component in providing adequate medical care.\textsuperscript{201}

**D. Kantian Obligations**

A third line of non-utilitarian reasoning stems from Kantian moral theory. In some respects, this is the most interesting, because commentators frequently assume that research with IAs is fundamentally at odds with Kantian deontology. More specifically, they assume that research that is not combined with therapy ‘is inherently in contradiction to the much vaunted respect for all individuals’.\textsuperscript{202} This assumption is usually due to an oversimplification of the principles attributed to Kant that individuals should not be used solely as a means\textsuperscript{203} and that an act is not moral unless it is independently willed. If these principles were intended to mean that nothing may be done to individuals without their prior consent or the consent of a personal representative,

\begin{itemize}
\item \textsuperscript{198} Although it is not possible to secure the informed consent of adults lacking capacity, it is possible to follow decisions made before they lost capacity or to ask a proxy who knows them well for substituted consent.
\item \textsuperscript{199} Ackermann, \textit{op.cit.}, n.198, 875.
\item \textsuperscript{200} The obligation of beneficence does not mean that all risk should be avoided (this would be impossible); it means serious risk must be avoided.
\item \textsuperscript{201} Ackermann, \textit{op.cit.}, n.198, 878–879.
\item \textsuperscript{202} S. McLean, and S. Elliston, \textit{op.cit.}, n.195, 8.
\item \textsuperscript{203} \textit{Ibid.}, 10.
\end{itemize}
Kantians would reject public health interventions or other policies that redistribute public goods without consent. 204 O’Neill’s work immediately casts doubt on that conclusion. 205 The key to a proper understanding of the Kantian view of medical research is to appreciate the Kantian concept of autonomy.

O’Neill explains that Kantian autonomy is very different from the standard bioethical understanding that portrays autonomy as an entitlement to independence and the freedom to make subjective choices. Unlike this conception (which O’Neill calls ‘individual autonomy’), Kantian autonomy is an obligation to reason rationally; more specifically, an obligation to live a life according to laws or principles which could be chosen by all or, in other words, according to reasons that are acceptable to other rational beings. 206 O’Neill terms it ‘principled autonomy’. It flows from the idea that moral acceptability, indeed moral worth, is grounded in the exercise of reason. The Kantian notion that we should respect the autonomy of others is thus an exhortation that we should respect the principled autonomy of others or, in other words, their rational decisions.

The principles that comprise ‘principled autonomy’ are constrained by the idea that they should be universalisable 207 and not self-defeating. 208 Following the idea that autonomy is an obligation, they are formulated as obligations (rather than rights or interests). The best known principle is the obligation not to deceive or coerce other individuals. Deception cannot be universally willed because it would undermine individuals’ capacity for autonomous action. It would also be self-defeating because people would quickly learn that they could not rely on other people’s statements and so the lies would not be believed. 209 A less familiar principle of principled autonomy is the obligation to support and assist others who are vulnerable even where it exposes people to risks that they themselves have not elected. It follows because we cannot commit ourselves to a universal principle

204 Many other public programs for health, education, housing and jury service (to name but a few) would also be inherently un-Kantian, as they are organised without the consent of all those who contribute to them.
207 A rational person realises that, all things being equal, he cannot regard himself as being permitted to act in ways that are forbidden to others because other citizens would not accept this, furthermore, if others took the same attitude his interests would be curtailed.
208 Identifying these principles is the most difficult and contentious step in Kantian reasoning.
that puts everyone’s, including our own, survival and quality of life at risk.\textsuperscript{210} This is the basic groundwork for O’Neill’s views on public health ethics:

Although [the rejection of indifference] cannot require any individual to render \textit{all} needed assistance to \textit{all} others in \textit{all} predicaments (an impossibility), it demands more than the sporadic meeting of others’ needs, for example, by the episodic charitable donations or emergency aid... [In most circumstances] it is best expressed by supporting social and political institutions and practices that reliably reduce and limit vulnerability by providing a reliable degree of security and subsistence for all, for example by arrangements that help make food and health care affordable and the environment safe.\textsuperscript{211}

These ideas have major implications for the governance of medical research. The first implication is that an individual’s consent is not absolutely essential to justify research. Although consent mechanisms can be a way to respect another person’s autonomy, Kantians are not wedded to the idea of respecting an individual’s ‘mere, sheer choice’.\textsuperscript{212} An irrational, unprincipled granting or withholding of consent is not held in high regard. Kantians also refrain from insisting that an individual’s choice be ascertained for every punctuate decision. Autonomy is an obligation which should be met in general and over the course of a life, not necessarily every instant.\textsuperscript{213} They also point out that principled autonomy ‘is expressed in action whose principle \textit{could be adopted by all others}; thus it is not always necessary to ask for \textit{actual choices} to be made.\textsuperscript{214} To reassure individuals that they are not being coerced or deceived into unprincipled action, it is possible to set up other institutions or practices to monitor the activities. Finally, it must be said that the idea that we should respect the autonomy of an IA (\textit{i.e.} treat them as an end in themselves) can be nonsensical to a Kantian because the IA has no rationality to respect. This is not to say they will be treated with disregard. Other persons are expected to support their capacity for rational action so far as possible.

\textsuperscript{210} O’Neill, \textit{op.cit.}, n.207, 88.
\textsuperscript{211} Ibid., 88–89.
\textsuperscript{214} In fact, consent procedures can be problematic where they give unconditioned priority to directionless, unreflective choices regardless of the needs of other people: O’Neill, \textit{op.cit.}, n.207, 85.
(e.g. to provide special forms of communication and, where possible, proxy-decision-making) and to follow precepts of principled autonomy, which protects them from serious harm or indifference.

The second implication—which follows from the rejection of indifference—is that rational beings are morally obliged to support research activities that work towards safe, effective health care if the risks are not serious. Today’s patients benefit greatly from the medical discoveries of yesterday and thus know the importance of altruistic participation in research. It would be irrational for them to reject a weak Samaritan principle. A permanently incapacitated IA does not owe an obligation in the same way (since autonomy is an obligation to act rationally), but it is rational for others to protect them from serious harm only. So, in effect, a Kantian could be expected to agree that a policy based on cooperation is better than conscription, but that limited exceptions are permissible where the efforts to seek the individual’s view, or the view of their personal representative, are highly impractical or impossible and the patient-subject has not actively refused.

It is not our intention to argue that Kantian or other deontological reasoning is superior to utilitarian reasoning. Nor do we say that all Kantians reason in the way we have described. Our point is that the ethics of research involving IAs is not dependent on utilitarian reasoning. Provided it is properly conditioned, there are several established lines of ethical reasoning that regard it as being consistent with respect for the equality of persons, human dignity and individual integrity as well as serving the public interest. Unless all these diverse lines of reasoning are to be dismissed—and another theory shown clearly to be preferable—laws and proposals that facilitate research with IAs subject to strict conditions and oversight deserve more than the ambivalent support they currently receive.

V. CONCLUSION AND RECOMMENDATIONS

Although the European medico-legal community understands the need to protect IAs involved in research and the link between research and new technology, it seems less aware that research is essential to protect IAs as a population and to discover whether therapies currently in widespread use are safe and effective. If this were appreciated, the tendency to regard research as fundamentally different and less important than treatment, clinical audit and public health monitoring would not be as strong. The community also seems ignorant of the fact that the evidence base for the treatment of conditions affecting IAs is rudimentary, and that the desultory outcomes we take for granted could be significantly improved. Furthermore, it has a hazy understanding of the differences between medical treatment and research, and has not yet
appreciated how these differences might be transposed into research governance. It continues to think a distinction between research with and without individual benefit, with the latter more heavily regulated, will protect IAs. Most significantly, we have not been particularly systematic in our efforts to discover how regulation could better integrate strong, reliable protection with a positive and vigorous scientific culture. More generally, Member States continue to struggle when they try to harmonise national laws that cut across issues of high moral controversy. Unfortunately, these confusions permeated the development of the CTD, particularly Article 5. Although it will undoubtedly improve the level of protection guaranteed to human subjects in European research, especially in countries where there was previously no specific regulation of clinical trials, it will present serious difficulties for efficient and effective research if transposed in a literal fashion.

Our aim in this article was to highlight the potential pitfalls and to help disentangle the conceptual confusions. We have suggested ways in which the CTD could be interpreted to better balance and harmonise European laws. We appreciate that our proposals would not find favour if they were premised purely on a utilitarian ethic, but we have endeavoured to show that our arguments are supported by other ethical theories and internationally respected laws, reports and declarations.

In summary, we have argued that research involving IAs should be based on a good scientific case, including sound prior research, clinical equipoise and sensible methodology. It should occur only when there are no alternative means to carry out the research without involving incapacitated persons, and the benefits to society are broadly proportionate to the risks to the individual. It is also important to abandon the notion that ‘therapeutic research’ is ‘better’ than non-therapeutic research, turning instead to component risk analysis. In this framework, the research risks (including physical, psychological and social risks) must be minimal, minimised and monitored. We also support the need for procedural safeguards including ethics committee review (by independent people who have the knowledge and experience to ascertain whether the risks are reasonable and proportionate) and, where contactable, review by a representative who knows the individual and can thus attempt to reason as the individual would. Together, these requirements respect the autonomy of the individual (so far as possible), provide an environment for improving medical standards, ensure that harm and infringements of privacy are minimal or non-existent, insist researchers abide by professional obligations to act beneficently and in the best interests of patients and protect vulnerable patients as people with equal rights to privacy, dignity and well being.
To achieve this, we have outlined various recommendations. The most important include: (a) implementing legal provisions (and associated guidelines) that allow consent to be waived in emergency research and support clinical equipoise; (b) encouraging clear risk analysis as described by Weijer and Miller and endorsed by NBAC; and (c) supporting swift, specialist, on-going review by ethics committees that is neither conservative nor cavalier. The legal system would then better protect IAs involved in research, the ethos of the medical profession and future IA patients.

215 For the list of recommendations submitted to the European Commission as a result of our research: op.cit., n.1, 7–8.