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I. Background and Introduction

The efforts of the ICH[1] in the harmonization of rules for clinical trials has been at the heart of the move towards the globalization of pharmaceutical development in the last hundred and fifty years. The chief driving force for this is the desire to increase "the efficiency of the process for developing and registering new medicinal products in Europe, Japan and the United States in order to make these products available to patients with the minimum of delay."[2]

The work of the ICH, therefore, focuses on minimizing regulatory and

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1. The International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use. References to ICH documents follow the new codification system for ICH Guidelines adopted in November 2005.
2. ICH, *Statement by the ICH Steering Committee on the occasion of the Fourth International Conference on Harmonization, 16-18 July 1997, Brussels,* and *The Future of ICH – Revised 2000: Statement by the ICH Steering Committee on the occasion of the Fifth International Conference on Harmonization, 9-11 Nov. 2000, San Diego.* The excerpt quoted appears in identical form in both documents.

bureaucratic obstacles to the recognition by one jurisdiction of clinical trials conducted in another for the purpose of securing approval for a drug in the all of the jurisdictions party to the ICH. Of the various guidelines thus far issued by the ICH, the most significant is ICH-GCP E6.[3]

Although ostensibly directed at the objective of promoting the mutual recognition of clinical trials by the regulatory authorities party to the ICH,[4] the real impact of ICH-GCP E6 traverses far beyond its relatively modest official ambitions and intended target partner jurisdictions.[5] The reality is that in the absence of any other similar internationally-accepted set of guidelines for the conduct of clinical trials, ICH-GCP E6 has become the *de facto* international standard for the conduct of clinical trials.

This situation is underscored by the fact that the member jurisdictions of the ICH account for "the vast majority of new medicines are currently developed,"[6] so that even countries with no direct formal representation in the ICH feel pressure to adopt (or adapt) ICH standards as their own. The alternative is to be cut off from collaboration with researchers from direct ICH party jurisdictions and to be excluded from participation in multicentre trials involving researchers from direct ICH party jurisdictions.

The case of Singapore is an example. Like many economically successful developing countries in the Asian Pacific Rim, it is eager to foster a biomedical sector of its own. This necessarily implies the development of a broad-based clinical research industry with the hope of increasing technology transfer from scientifically advanced jurisdictions through collaboration in trials. This in turn requires clear standards and guidelines for the conduct of clinical research acceptable to research partners in Europe, Japan and the United States. For

3. ICH, *ICH Guideline for Good Clinical Practice* E6(R1) [Current Step 4 version dated 10 June 1996] [hereinafter *ICH-GCP E6*]. The term "clinical trial" is used in this article in the sense as defined in ICH-GCP E6[R1] 1.12. In essence, clinical trials are research programs in which prospective new drugs (or existing drugs for new purposes) are tested on human subject volunteers for safety, quality and efficacy. Clinical trials are therefore a subset of the wider field biomedical research which involves the use of human subjects (which broader field is referred to in this paper as "research involving human subjects").
4. *See* ICH, *Structure of the ICH* for background on the ICH Parties, *available at* http://www.ich.org/cache/compo/276-254-1/html.
5. Europe, Japan and the United States: *Cf.* ICH, *History and Future of ICH*, *available at* http://www.ich.org/cahce/compo/276-254-1.html. Significantly, "Europe" in this context extends to all the countries of the EU through its representation in the ICH through the European Commission. Some non-EU European countries are accommodated through the Europe Free Trade Area (EFTA) having official observer status in the ICH, which status is also held by the World Health Organization (WHO) and Canada.
6. ICH Statements, 1997 and 2000.

developing countries seeking collaboration with developed countries, there is, theoretically, a choice between the ICH-GCP E6 model and the similar (but not identical) document proposed by the World Health Organization (WHO).[7] Given the realities of the situation, however, it is not surprising that the current Singapore Guideline for Good Clinical Practice (SGGCP) is explicitly adapted from ICH-GCP E6.[8]

The original aims and *raison d'etre* of the ICH (harmonization of rules in member countries) obviously have no direct application to Singapore and other small countries with biomedical ambitions. Instead, an essentially procedural document drafted for one purpose (for the technical purpose of harmonization of existing procedures) has been harnessed for quite a different purpose: to be transformed into a set of substantive rules to be applied in itself.

In this paper, I will explore consequences of and implications to this process of translation, some of which are only now being realized. In the treatment of legal issues, I adopt the perspectives of the common law of Singapore and England, which are identical for all the issues discussed.[9]

II. The Issue of Consent

A. Consent and the Road from Nuremberg

For countries like Singapore, there is little doubt that ICH Guidelines like ICH-GCP E6, provide a valuable foundation not only for local rules governing the conduct of clinical trials, but also for other forms of research involving human subjects. In Singapore, for example, the national Bioethics Advisory Committee recently issued a set of Guidelines for the governance of research involving human

7. The World Health Organisation, *Guidelines for Good Clinical Practice (GCP) for Trials on Pharmaceutical Products* (1995), WHO Technical Report Series, No. 850, 1995, Annex 3.
8. Ministry of Health, Sing., *Sing. Guideline For Good Clinical Practice (SGGCP)* (2001), which acknowledges on its title page that it is adapted from E6. In turn, the SGGCP is given formal standing by Regulation 21 of the Medicines (Clinical Trials) Regulations (S54/78) promulgated under Section 18 of the Medicines Act (Chapter 176). The full text of all Singapore statutes (e.g. the Medicines Act, but not subsidiary legislation or regulations such as the Medicines (Clinical Trials) Regulations) *available at* http://statutes.agc.gov.sg/.
9. Singapore is a former Crown Colony of Great Britain, and inherited its legal system (and a great body of statutory law) from its former colonial masters. Even today, some English statutes continue to have application in Singapore. For historical reasons, the reception of English law into Singapore is a complex inquiry, but it suffices here to note that English common law in this area is applicable to Singapore by virtue of Section 3 of Singapore's Application of English Law Act (Chapter 7A).

subjects (other than clinical trials) entitled *Research Involving Human Subjects: Guidelines for IRBs*.[10] Notably, these Guidelines draw their inspiration from the principles and structures set out in ICH-GCP E6. In particular, the Guidelines look to the sections establishing and setting out the roles and responsibilities of institutional review boards (IRBs)[11] and investigators.[12]

In matters of consent, the ICH-GCP E6 guidelines focus on process[13] rather than substance. While it makes clear that the "[f]reely given informed consent should be obtained from every subject prior to clinical trial participation"[14] and goes into considerable detail as to the formalities of obtaining and documenting such consent,[15] the documents shy away from mentioning the required substance and the ethical basis of such consent, beyond requiring that "clinical trials . . . be conducted in accordance with the ethical principles that have their origins in the Declaration of Helsinki."[16] The first point of inquiry in this paper is whether this application of the Declaration of Helsinki is entirely appropriate.

At first sight, it may seem that the Declaration of Helsinki[17] is a natural fit with the ICH-GCP E6. However, there is a fundamental disconnect between the intent of these two documents. In spirit, the Declaration Helsinki is an elaboration and further development of the ethical principles espoused by the Nuremberg Code[18] which is considered the first formal articulation of the ethical obligations of researchers to human experimental subjects in research trials.[19] The central theme

10. The Bioethics Advisory Committee (BAC), Singapore, Nov. 2004, *available at* http://www.bioethics-singapore.org/resources/reports3.html in full text. The BAC is a national panel appointed by the Government to advise it on "potential ethical, legal and social issues arising from biomedical sciences research in Singapore." The author is a member of the BAC. However, all views expressed in this article are to be taken strictly as his own.
11. ICH-GCP E6, *supra* note 3, ¶¶ 3.1 to 3.4.
12. *Id.* at ¶¶ 4.1 – 4.13.
13. It may be of note that the ICH-GCP E6 begins its definition of the term "Informed Consent" with the words "A *process* by which a subject voluntarily confirms his or her willingness to participate . . . "(emphasis added).
14. ICH-GCP E6, *supra* note 3, ¶ 2.9.
15. *Id.* at ¶¶ 4.8.1 to 4.8.15.
16. *Id.* at ¶¶ 2.1, 4.8.1.
17. The World Medical Association (WMA), *Declaration of Helsinki: Ethical Principles for Medical Research Involving Human Subjects* 2004, *available at* http://www.wma.net/e/ethicsunit/helsinki.htm [hereinafter Declaration of Helsinki].
18. "Trials of War Criminals before the Nuremberg Military Tribunals under Control Council Law No. 10," Vol. 2, 181-2. Washington, D.C.: U.S. Government Printing Office, 1949.
19. The connection between Helsinki and Nuremberg is not as direct as it may seem: it is likely that the WMA would have eventually established guidelines for the ethical governance of research involving human subjects even without the horrific example of the conduct of certain German doctors during World War II. For a discussion of this, *see* D. Human & S.

of both Nuremberg and Helsinki is the ethics of research involving human subjects. But there is another equally important corollary to this central theme: the role and the ethical responsibilities of the *physician* as an investigator in a trial involving human subjects. Therein lies one point of disjuncture. Quite understandably, the WMA assumes the perspective of physicians, and the implied context of the Declaration of Helsinki applies the ethical language of the physician-patient relationship. It articulates a *physician*'s duties are to his patients. Thus, the first three paragraphs of the Declaration of Helsinki affirm the central obligation of physician for the health and welfare of his patient, and by extension, for any human subject.

The relationship between a physician and his patient and the relationship between a researcher and his subject, however, are far from analogous. Yet it seems strange that the research community appears to have adopted lock, stock and barrel a concept that was first developed for quite a different context and relationship: that of the physician-patient, and not that of the researcher-subject.

Many physician-researchers do not appreciate that the two relationships are very different and have completely different foundations in ethics and law. In the physician-patient relationship, the consent transaction is mutual: the patient agrees to assume a risk against the hope of improving his health. There is not the same assumption and promise of mutuality in the researcher-subject relationship, and in the vast majority of cases there can only be risk without any hope of benefit. The argument is that information presented in the physician-patient context has at least the common objective of the hope of achieving a certain outcome, and thus, the context of the information presented is clear. But what common objective can exist in the different context of researcher-subject? If the paramount guiding ethical principle for the physician is *primum non nocere*, the problem is that there must *always* be a fundamental conflict when a physician engages in research, particularly where his own patients are involved as subjects in the trial.[20] This is because medical research *always* carries with it a risk of harm, even if the likelihood of such harm is remote, or even if the nature of the harm is likely to be trivial.[21] The inherent nature of this fundamental conflict between these two

Fluss, *The World Medical Association's Declaration of Helsinki: Historical and Contemporary Perspectives*," (World Medical Association, 2001), *available at* http://www.wma.net/e/ethicsunit/pdf/draft_historical_contemporary_perspectives.pdf.

20. As clearly contemplated by the provisions of Part C of the Declaration.
21. *See generally* BAC's *Research Involving Human Subjects: Guidelines for IRBs, supra* note 10, at ¶¶ 3.5–3.7 (indicating that not all harms potentially posed by participation in a trial need be of a physical nature).

distinct relationships is at the heart of the on-going controversy and debate within the World Medical Association over the revision of paragraph 30 of the Declaration of Helsinki as to whether patients enrolled as trial subjects have a right to "the best proven prophylactic, diagnostic and therapeutic methods identified by the study."[22]

At the heart of the both the physician-patient relationship and the researcher-subject relationship is the concept of the voluntary assumption of risk through consent. But while the assumption of risks can be fairly readily justified from the ethical perspective in the physician-patient relationship by the *mutual* objective of direct benefit to the patient, the same risk-benefit analysis cannot be applied to the researcher-subject relationship, where this mutual objective of benefit to the subject is absent. Researchers have to appeal to rather more indirect and larger benefits which relate not to the subject but to society at large. Instead, the bargain has to be couched in uncomfortably vague terms, such as that "[m]edical progress is based on research which ultimately must rest in part on experimentation involving human subjects."[23]

A further point of distinction between the two kinds of relationships (physician-patient and researcher-subject) is that unlike the physician, the researcher, in most cases, stands to benefit directly from the risk untaken itself: without the risk, there is no possibility of benefit to the researcher, and there can be no trial.[24] This is a point which both ICH-GCP E6 and the Declaration of Helsinki do not detail, except obliquely when dealing with the point of conflict of interests.

Both the ICH-GCP E6 and the Declaration of Helsinki are careful to cast the researcher-subject relationship in terms of a bargain in which the risks have been carefully considered by the researchers, with the researchers being under an obligation not to embark on the trial at all (much less recruit subjects) if the "predicted" or "anticipated" risks outweigh the potential benefits.[25] It is a two-

22. *See* World Medical Association, *WMA Secretariat Report on the Revision of Paragraph 30 of the Declaration of Helsinki* (2003), and World Medical Association, *The Workgroup Report on the Revision of Paragraph 30 of the Declaration of Helsinki* (2004), both *available at* http://www.wma.net/e/ethicsunit/helsinki.htm.
23. Declaration of Helsinki, *supra* note 17, ¶ 4.
24. Not only in terms of the researcher being paid to conduct the research, but also in terms of access to research funds, academic reputation, and potential direct monetary gain through a commercially useful discovery. In contradistinction, it may be argued that a physician generally is (or should be) paid his fee, irregardless of whether the patient decides to assume the risk proposed: the job of the physician here is find out what choices there are for the patient, and to assist the patient in making a choice.
25. The ICH-GCP E6 states categorically that a "trial should only be initiated and continued only if the anticipated benefits justify the risks" (ICH-GCP E6, *supra* note 3, ¶2.1), while

stage risk-benefit analysis: first the researchers must confirm that the predicted or anticipated risks do not outweigh the benefits, and then (and only in such circumstances) may they propose participation to a potential subject, who has to make his or her own decision about whether to assume the risk or not. Neither document is very clear, however, as to what kind of "benefit" is to be weighed against the risks. The ICH-GCP E6 is silent on this point, while the Declaration of Helsinki merely speaks of "foreseeable benefits to the subject or to others." What if, for example, the only foreseeable direct benefit is to the investigator and the sponsor, and indirectly to larger society, and no direct benefit exists to the subject, who must bear all of the risk of harm?

From the ethical viewpoint, perhaps the most difficult aspect of this relationship is the hard fact that the subject is essentially being asked to assume *unpredictable* risks. To pretend otherwise would be unethical: if the risks were perfectly predictable and quantifiable, there would be no need for clinical trials. The very purpose of trials (especially Phase I and Phase II trials) is to pinpoint and quantify the very risks which the subject is being asked to assume. The recent incident involving the experimental monoclonal antibody TGN1412 is a sobering reminder of the true nature of this point. In that incident, all six healthy volunteer subjects who were given TGN1412 on 13 March 2006 developed serious reactions to the drug. This reaction was not anticipated because no such response was present during the animal testing phase of the trial. In its final report on the incident, the responsible regulatory authority, the UK Medicines and Healthcare Products Regulatory Agency (MHRA), came to the conclusion that "an unpredicted biological action of the drug in humans is the most likely cause of the adverse reactions in the trial participants."[26] The design and the administration of the trial were not at fault. Rather, the unpredictable biology of the human body was to blame for such reaction. This unpredictable human biology, however, was the very object of the investigations in that clinical trial.

Taking these points into consideration, the fundamental difficulty with the ICH

the Declaration of Helsinki requires that every trial "involving human subjects should be preceded by careful assessment of predictable risks and burden" (Declaration of Helsinki, *supra* note 17, ¶ 16).

26. The UK Medicines and Healthcare Products Regulatory Agency (MHRA), *Investigations into Adverse Incidents During Clinical Trials of TGN1412* (released 25 May 2006), *available at* http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2023821&RevisionSelectionMethod=LatestReleased). *See also* the Interim Report of the MHRA (also bearing the same title, but released 5 Apr. 2006, *available at* http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2023519&RevisionSelectionMethod=LatestReleased).

using the Declaration of Helsinki as the basis of the ethical principles to be applied in clinical trials is simply that the Declaration of Helsinki is a document drafted from the perspective of a profession in a fundamentally different relationship to the people with whom they must deal. Physicians take risks (with their patients' consent) for the direct benefit of their patients while researchers do not. If TGN1412 had been given as an experimental drug of last resort to severely ill patients who might have benefited from it, the ethics of the situation would have been completely different. The risk-benefit analysis would have been examined in the context of quite a different relationship: that of the physician and patient and not that of the researcher-subject.

It may be that from an ethical viewpoint, it is permissible for a severely-ill patient with limited treatment options to accept far more risks from an unproven drug or intervention, than would be permissible for a otherwise healthy volunteer. The point then is that the ethics applicable to the two different relationships (of physician-patient, and researcher-subject) are not and cannot be the same. To confuse the two relationships carries with it many difficulties. To say that a researcher has the same or similar kind of ethical obligations to his research subject as a physician does to his patient is to obscure the true nature of the relationship. When a physician acts as a researcher, the difference in capacity should be made abundantly clear to the patient-subject. This is the confusion of roles has led to the controversy over the revision of Paragraph 30 of the Declaration of Helsinki.

There is a legal implication to the difference between the two kinds of relationship described above, particularly in the context of Singapore and England. In both Singapore and England, the courts have firmly refused to admit the doctrine of informed consent. As held in *Canterbury v Spence,*[27] a failure to fully inform a patient of *all* the potential risks and consequences of a propose course of therapy goes to an action in trespass (for battery on the grounds that the patient did not consent to the interference) rather than to an action in negligence.[28] Such a refusal to admit the *Canterbury* doctrine has had the effect of making it much more difficult for patients with iatrogenic injuries to succeed in a claim than if they were allowed an action in trespass, given that they would have the added burden of proof of causation and damage in the action of negligence. In Singapore, the Court

27. Canterbury v. Spence, 464 F 2d 772 (1972).
28. Sidaway v. Board of Governors of the Bethlem Royal Hospital, [1985] A.C. 871 (House of Lords) – the majority of the Law Lords refused Lord Scarman's impassioned plea for the reception of the `American' doctrine of informed consent.

of Appeal has conceded that the result of one of its decisions has been "to confer near-immunity to the medical profession from actions in negligence."[29] The implied basis of this presumption or bias in favour of the medical profession in Singapore and England is based at least in part on the perception or assumption that a physician undertakes risks not for his own benefit but for the benefit of his patient.[30]

In *Sidaway v. Board of Governors of the Bethlem Royal Hospital*, Lord Diplock, writing for the majority, observed that "inevitably all treatment, medical or surgical, involves some degree of risk that the patient's condition will be worse rather than better for undergoing it."[31] Needless to say, this analysis cannot apply to the researcher-subject relationship: except in the case of therapeutic trials (when the investigator will almost certainly be a physician), the taking of the risk can never be of direct benefit[32] (and indeed only potential harm) to the subject himself. From this point of view (although this is not an area of law which has been explored by the courts in either jurisdiction), it is unlikely, therefore, that the Singapore or English courts would view any deficiencies or inadequacies in the consent process in clinical trials with the same indulgence as with consent in the context of the physician-patient relationship.

Increasingly, biomedical research is being carried out around the world not by physicians (or at least by physicians acting in their capacity as physicians) but by researchers who are not physicians. Arranging for and conducting clinical trials has long become a lucrative business by itself. In such a situation, the limitations of the Declaration of Helsinki, with its focus on the obligations of physicians, become especially obvious. Now more than ever, there is a pressing need for the research community to come out of the shadows of the physician-patient relationship and define the ethical basis of the researcher-subject relationship in its own right. This ethical basis should not only be defined in terms of the relationship between the researcher and the subject, but in terms of the rights and obligations that arise between various other parties such as the attending physician (if he is not also the researcher), the sponsor, the clinical trial agency, and the approving IRB. There are many more parties involved in a clinical trial than in the clinical practice setting, and it is important that the mutual relationships of the various parties are clearly articulated in ethical guidelines and the law. The ICH

29. Dr Khoo James and Another v. Gunapathy d/o Muniandy, [2002] 2 SLR 414; [2002] SGCA 25, at ¶ 58.
30. *See generally Dr Khoo James*, at ¶ 144.
31. *Sidaway*, at 890.
32. Except monetary benefit.

guidelines are a start in this direction in defining the roles of parties such as IRBs, Sponsors, Contract Research Organizations, investigators and subjects and their relationship to each other. What is now needed is a document that defines the ethical basis of these emerging relationships on their own terms instead of referring them to an essentially irrelevant paradigm, that of the relationship of physician and patient.

B. The Reification of Consent

As already noted, the concept of "informed consent," is one concept so fraught with legal and ethical difficulties that it is open to quite different interpretations in different jurisdictions. It will probably not surprise American legal scholars that "[e]nglish law does not accept the transatlantic concept of 'informed consent.'"[33] How this concept, so fundamentally rooted in the physician-patient relationship and its assumptions (most of all, the assumption that a physician takes risks, with the patient's consent, for the *benefit* of the patient), can be transplanted into the different relationship of researcher and subject has yet to be fully explained.

Yet the assumption in the ICH documents is that not only is this concept of "informed consent" universal (applying to all jurisdictions), but it can be taken from the context of one relationship and transferred lock, stock and barrel to another. The ICH-GCP E6 defines "informed consent" in terms of information on "all aspects of the trial that are relevant to the subject's decision to participate."[34] Potential subjects are to be given information on "reasonably foreseeable risks,"[35] but significantly, there is no obligation on the part of the researcher to make a substantive assessment as to whether the subject fully appreciates the risk or has misinterpreted the information provided. The main obligation of the researcher is to provide the required standard information and record the written consent of the subject.[36] The Declaration of Helsinki only requires that an investigator ensures that the subject "has understood the information,"[37] but not that the subject has a proper or objective appreciation or interpretation of the risks as disclosed by the information presented. In contrast, a physician is under an obligation not only to present the information, but to ensure that the risks have been understood correctly

33. Lord Donaldson *In re T. (Adult: Refusal of Treatment)* [1993] A.C. 95, 115 (Fam. 1992). By extension, the same rule applies to Singapore.
34. ICH-GCP E6, *supra* note 3, at ¶1.28.
35. *Id* at ¶4.8.10(g).
36. *Id.*
37. *Id.* at ¶22.

and appreciated in their proper context.[38]

Perhaps even more fascinating is the way that the concept and requirement of consent has been formalized in the culture of research. One of the things that students struggling with bills of lading, letters of guarantee, and letters of credit quickly learn is that banks are required to deal only with paper; they are not concerned with, the underlying substance of transactions, and look only to strict fulfillment of the agreed procedure or conditions.[39] Unfortunately, there is more than an echo of this process of reducing a substantive inquiry into a merely procedural documentary process developing in the world of biomedical research. One of the more unfortunate consequences of the ICH-GCP E6's pre-occupation with process is that the consent requirement tends to be reified and reduced to a liminal function. In the methodology of science there is often a tendency to want to see things in black or white, whether something is present or not. Reduced to its barest parts, this liminal approach treats consent as a checkpoint, which once satisfied, opens the door to the next step in the flow chart. Once "obtained," it needs (and indeed admits) no further revisiting.

There is often a strong temptation to bring the conventions and reflexes of the scientific method to the world of bioethics, which unfortunately is constructed out of a human and infinite palette of moral choices and not in the binary format preferred by scientists. Likewise, there is often strong pressure for the terms of the consent to be standardized: no IRB will allow for consents to be framed in different terms for different subjects when they are part of the same trial and subject to the same kinds of risks. Yet surely it cannot be that research subjects are all equally satisfied and accepting of the risks to be undertaken by them or that they have the same appreciation of the risks or of their own individual physiological response or vulnerabilities to the proposed investigations, or share

38. An especially lucid statement of this may be found in the UK Royal College of Pathologists' *A Brief Guide on Consent for Pathologists* (Jan. 2005), *available at* http://www.rcpath.org/. Paragraph 2 especially makes clear the obligation of a person taking consent not only to deliver information, but also to assess "the patient's understanding of the information and of the issues involved" as well as an "appreciation of the consequences of a course of action". It notes soberly that clinicians "often find it difficult to know how much information to offer in this context, since it is difficult for patients to judge the likelihood or severity of a wide range of possible outcomes" (Paragraph 2.1(iii)). A similar approach is advocated by the UK General Medical Council (the UK body having responsibility for the licensing of physicians) in its Guidance entitled *Seeking Patients' Consent: The Ethical Considerations* (Nov. 1998), and *Research: The Role and Responsibilities of Doctors* (Feb. 2002); both *available at* http://www.gmc-uk.org.

39. The International Chamber of Commerce, *ICC Uniform Customs and Practice for Documentary Credits* (ICC Publication No. 500, 1993) Articles 3 and 4. *See also* U.C.C. §5-108(f) and (g)(1997).

the same kind and degree of concerns about the risks.

In this respect, there is a fundamental difference between the consent that trial subjects give and that patients give. Every physician appreciates that the consent given by a patient to treatment cannot be standardized, but must be tailored and be dependent on the condition of the patient, the treatment choices open to the patient, *and* the progress (or otherwise) of the agreed course of treatment. Through every step of the agreed course of treatment, the consent of the patient must be continually revisited: now that we have done this, and the results are that, should we continue as originally agreed, or should we talk about what else could be done? The terms of consent of patients are therefore uniquely tailored to each patient's condition, and are revisited constantly.

This is simply not the practice in relation to research subjects. In most cases, subjects are simply given a standard account of the risks (i.e. all the subjects in a given trial are presumed to be exposed to the same or similar level and type of risk, regardless of their actual individual physiology),[40] and in return, are asked to give their consent in equally standard terms. Yet consent is clearly something which can never be absolute, or truly standardized, any more than the unpredictable human biology and physiology which the clinical tests seek to explore. To a biomedical researcher, consent may be something that proves that the subject has abandoned any objection to the proposed intervention. But perhaps one might better describe consent as simply recording the outcome of a very peculiar transaction, which records the intent of the parties in a very one-sided fashion. Effectively, the subject is told to simply answer "yes" or "no" in a dialogue the script of which is entirely framed and written by those seeking the consent. It is essentially a record of a one-way conversation: these are what we think are the risks, do you understand, and do you agree? There can be no provision for exclusions, reservations, or expressions of concern about particular aspects of the trial or any non-standard record of the subjects' responses. It is all or nothing.

But what is the alternative? The difficulty is that while it is easy (and appropriate) for a physician to treat every consent as being the unique expression of individual patients and to tailor his or her response as a physician accordingly, this course is not open to researchers who must ultimately serve the cause of a trial and not the individual interests of subjects. For the researcher, standardization is a

[40] The alternative to a standardized account would be to give the potential subject an account of the risks specifically tailored to the medical history and profile of the potential subject. This would necessitate an unrealistically exhaustive medical examination and investigation which few trials could afford, even assuming that an IRB could be persuaded to accept the resulting subjectivity of the risks to be communicated to each individual.

key plank of the trial and of the validity of the results. While accepting that the unsatisfactory answer is that there may be no answer to this difficulty, the point may be made that this again is yet another reminder that the concepts of risk and consent in the context of researcher and subject cannot be equated with that in the context of physician and patient. It if is, we run the risk of reifying consent and reducing it to a purely legal requirement in which researchers deal only with paper instead of the substantive ethics and social bargain to which consents must ultimately relate. But it may be well for researchers to be more sensitive to consent not being simply a matter of providing standard information and obtaining a written standard response in satisfaction of a "legal" requirement.

C. Consent, Conveying Information, and the Lay Mind

In treating the requirement of consent in such a liminal way, biomedical researchers expose themselves to criticism even when acting in utmost good faith. Biomedical researchers assume a certain context in framing the information presented in the consent form. To put it another way, what the biomedical researchers assume they are conveying in the words of the consent form may not square with the understanding of even the best educated people simply because the information given by researcher may be interpreted by lay subjects from a very different perspective.

It is not necessary to go to exotic cultures and communities for an example of this. Consider the experience of the parents in the Bristol Royal Infirmary[40] and Alder Hey[41] scandals in England in the 1990s. In these incidents, parents signed consent forms allowing tissue samples to be taken for research from the bodies of their children who had died in the hospitals concerned. They thought that they were giving consent to small tissue samples. They did not contemplate that "tissue samples" might extend to whole organs, or entire blocks of organs.[42] In its Interim

40. The Royal Bristol Infirmary Inquiry, *Learning from Bristol: The Inquiry into the Management of Care of Children Receiving Complex Heart Surgery at the Bristol Royal Infirmary 1984-1995* (2001), Command Paper July 2001 (CM 5207(I)), and,*The Inquiry into the Management of Care of Children Receiving Complex Heart Surgery at the Bristol Royal Infirmary. Interim Report: Removal and Retention of Human Material* (May 2000), both *available at* http://www.bristol-inquiry.org.uk/.
41. The Royal Liverpool Children's Inquiry, *Report (Return to an address of the Honourable House of Commons dated Jan. 30 2001 for The Royal Liverpool Children's Inquiry*, *Report ordered by the House of Commons to be printed Jan. 30 2001* (2001)), *available at* http://www.rlcinquiry.org.uk/.
42. *Id.* at 369–71. At page 369, the Inquiry wrote that "[f]ully informed consent means that a person must have all the information required to form a final decision. It is not enough for clinicians to tell the next of kin that they would like to examine the body after death and this

Report on the removal and retention of human material, the Royal Bristol Infirmary Inquiry observed that the "word 'tissue' has come to be understood by some as a generic term including not only small sections of tissue but whole organs and parts of organs. This is not, however, how the term tissue is understood in everyday language. Indeed, most people would not regard organs as being properly described as tissue. Herein lies one of the many barriers to communication and understanding which are at the root of the problem we are examining.[43]"

It went on further to note that "while the pathologists and clinicians understood the word 'tissue' to refer to anything from whole organs to slides and frozen sections, the very great majority of parents had no appreciation of this."[44] Yet it appeared that at least some researchers assumed otherwise. The Royal College of Pathologists had to issue guidelines stipulating that "any tissue retained must match the relatives' perception of what they agreed to being retained, and its purpose."[45]

This has also happened in the context of a developed country. Language and culture was not in issue: those taking consent and those giving it shared the same language and culture (or thought they did). Yet there was a huge gulf between the understanding of the parties over the meaning of what the researchers thought they said and what the parents thought the researchers said. All this was over the interpretation of an apparently simple word and for a simple request for tissue. Consider how much more room there is for failure in modern clinical trials, where all the information required by 4.8.10(a)–(i) of the ICH-GCP may necessarily be of a highly technical nature and may run to many pages. The subject may think that he understands the *information*. But does he really understand and appreciate the information in the same way that the researcher does? And does (or indeed, can) the subject really understand and appreciate the *risks* implied by the information?

In the context of the globalization of pharmaceutical development, it will

might involve taking some tissue. The next of kin need to understand what is involved in a post mortem examination, including a description of whole body systems, removal of the brain and the steps necessary to remove various organs, no matter how distasteful the giving of this information might be to the clinician concerned," noting that (at page 370) "[u]ntil recently all Alder Hey consent forms referred solely to tissue. and not organs." It added that the parents affected were keen to see the hospital adopt a plain-reading definition of the terms "tissue" and "organ" as set out in the *Concise Oxford Dictionary*! *Cf.* also the case of "Samantha – 1 Month" (at pages 420, 421) and the assumption by her parents that "tissue" meant small tissue samples and not whole organs.

43. *Id.* at 2.
44. *Id.* at 13.
45. The Royal College of Pathologists (UK), "*Guidelines for the Retention of Tissues and Organs at Post-mortem Examination*" (Mar. 2000), at ¶ 5.2.

immediately be apparent how much more this problem of different contextual assumptions would be vastly compounded if biomedical researchers venture into communities and cultures of which they are not familiar. This is not to say that this cannot be done, or should never be done, but merely that these researchers should not assume that the definition of consent may not have the same meaning as it may have in their own country. And the information they present and the request made in the consent form, may likewise be received in ways not contemplated by the researchers. Researchers and subjects may well be on the same page, but may perceive different things from the same words.

D. Consent, Culture and Autonomy

In the West, it is not usually fashionable (or constitutional) to nakedly assert religious principles in matters of public debate. That simply does not hold in most of Asia where religion often asserts its right to a place at the table. In different cultures and societies, basic constitutional assumptions differ fundamentally, with equally fundamental implications for assumed contexts. Religious principles and values often underpinned some of the most fundamental responses in matters bioethical.

The standard model of consent familiar to most researchers in the West is premised on the notion of the complete autonomy of the individual to decide of his own free will what risks he chooses to assume. Yet in some Asian communities, such an assumption may not be entirely valid and must, in some cases, be applied with caution. In Singapore, a constitutionally secular society, there is a necessity for some accommodation for religious sensitivities in some laws.[46] For example, Islamic doctrine may require the consent of a male relative or heirs (known as a *wari*) in matters such as organ donation. This results in Muslims being excluded from the provisions of the Human Organ Transplant Act,[47] which provides for a presumed consent model for organ donation. In the case of Muslims, therefore, consent to organ donation cannot be presumed, although it is clear that Muslim religious doctrine in Singapore permits and encourages the donation of organs.[48]

46. A glimpse of the impact of multiculturalism on law in Singapore may be gleaned from an article written by the then Attorney-General, now the Honourable The Chief Justice of Singapore Justice Chan Sek Keong, *Cultural Issues and Crime* 12 S.Ac.L.J. 1 (2000).
47. Human Organ Transplant Act, as revised in 2004. The Act provides for a statutory presumption that a person dying in hospital consents to the donation of his kidneys, heart, corneas or liver for transplantation, unless he has previously indicated an objection. Human Organ Transplant Act, 1987, c. 131(a) (Sing.), at 5 (amended 2004), *available at* http://statutes.agc.gov.sg.
48. *See* the speech of the Hon. Member of Parliament Dr Ahmad Mohd Magad (Pasir Ris-

The sticking point, however, is consent: sometimes, in some contexts and in some cultures, a person may not have the kind of full autonomy over his or her body as a researcher from a different culture may expect, as the experience of Singapore in matters of organ donation demonstrates. There are other possibilities: information gleaned about a community from a study of blood samples may well be viewed by a given community as community property, and therefore it may not be open for any one individual to give that sample or information.

From the perspective of a researcher rooted in a culture which celebrates as sacrosanct the complete autonomy of the adult individual, such limitations on autonomy may seem objectionable. But the researcher should remember that this is not, in principle, any different from some societies deciding that parents may give consent for research on their children, never mind what the children might think. Or that the "legally acceptable representative" of the ICH-GCP E6[49] may give consent on behalf of others who may not be able to give it.

Also, there is the difficult question(legally, and especially ethically) of whether people in vulnerable or dependent situations should ever be recruited for trials. Here, the ICH-GCP E6 does provide some very useful guidance in its definition of "vulnerable subjects:"

> Individuals whose willingness to volunteer in a clinical trial may be unduly influenced by the expectation, whether justified or not, of benefits associated with participation, or of a retaliatory response from senior members of a hierarchy in case of refusal to participate. Examples are members of a group with hierarchical structure, such as . . . members of the armed forces, and persons kept in detention. Other vulnerable subjects include patients with incurable diseases, persons in nursing homes, unemployed or impoverished persons, patients in emergency situations, ethnic minority groups, homeless persons, nomads, refugees, minors and those incapable of giving consent.[50]

There is recognition in this definition that even in the most developed countries many individuals' freedom to make completely autonomous decisions for themselves fall far short of the theoretical norm. The question for the conscientious researcher is not whether such people exist in a given population (for they assuredly will), but simply to recognize them so that they may respond appropriately. There is, for example, practically universal agreement that children

> Punggol) on the Second Reading of the Human Organ Transplant (Amendment) Bill on 6 Jan. 2004: " When HOTA was enacted in 1987, Muslims were excluded because in the case of Muslims, according to the *Shariah* (or Islamic law), it is the *wari*s (or the inheritor), who has the right to decide what to do with the body of the deceased person and this is sacrosanct. Thus, it is not permissible to remove any organ from the cadaver without the prior consent of the *wari*s." (77 Sing. Parliamentary Debate, cols. 175-210 (Jan. 6, 2004).

49. ICH-GCP E6, *supra* note 3, at ¶4.8.
50. *Id.* at ¶1.61.

below a certain age do not have the same degree of autonomy to give consent as would adults of sound mind. But at what age? Here the universal agreement breaks down and the social values and norms of each society comes into play. Assessing and making judgments on such values and norms is a much more difficult endeavor than it may first appear, because it is a judgment which necessarily requires and assumes a great deal of intimate knowledge about unspoken social norms and structures within a given society. It is a task which becomes much more difficult when researchers venture into cultures and societies with which they are not familiar. Should they rely on their own assessments or should they leave these assessments to local experts and collaborators? The careful insistence in the ICH-GCP E6 on the use of the phrase "legally acceptable representative" in the context of obtaining consent begs the question of whether there should also be the corresponding concept of an "ethically acceptable representative." Ethics and law may not always complement each other in such matters.

The difficulty with the first approach is that methods and means of assessment of autonomy developed in the context and circumstances of one society may be ill-suited to be applied in another, especially where the language and economic circumstances are different. But, an honest attempt based on this approach is likely to be more sound and reliable from an ethical point of view than to simply delegate the task to "local experts," because such delegation may simply amount to a convenient abandonment of a non-delegable ethical duty. Cynical researchers may, for instance, find it convenient to simply delegate consent procedures to local collaborators on the plea that they "don't understand the language" or the culture—in the worst cases, in effect sub-contracting a core ethical and legal obligation to others. But delegation (even if it were legally and ethically acceptable) *assumes* that judgment of the impartiality and competence of the proposed "local experts" is in fact up to the mark, and that assessment that the ethical judgments of the local experts will be based on the same values as one holds. This is probably a far more difficult judgment to make than the first approach. But that is not to say that the views of local experts should be discounted: indeed, such views should always be (carefully) solicited, but they should be assessed and tested (for instance, by comparison with views solicited from other experts or collaborators) for probative value before they are taken into account.

E. Consent, Cultures and Making Moral Judgments.

About a hundred and thirty years ago, the US Supreme Court handed down a decision in *Bradwell v State of Illinois*[51] which most American legal scholars would prefer to forget. In its holding, the Supreme Court advanced reasons why it thought that it was just and right for the State of Illinois to deny a woman a license to practice as an attorney—her only disqualification being that she was a married woman. Justice Bradley, delivering the unanimous opinion of the Court, advanced reasons which would be indefensible today and would cause deep offense to most Americans. One of the ideas that Justice Bradley appealed to in defence of his decision was the old English common law idea of coverture, that "that a woman had no legal existence separate from her husband, who was regarded as her head and representative in the social state."[52]

I make no judgment of this decision. I shall only observe that it was an expression of the values of a society at a given time, in a given place, in the context of a given culture. Nor would most Americans judge their country of the 1870s to be immoral in holding to values which they find unacceptable today. I only mention the *Bradwell* decision because it may be useful in illustrating the potential pitfalls involved in a researcher making moral judgments about his study population, especially in relation to the validity of consent. Assume for the moment that a researcher was given the chance to go back in time to the Chicago of the 1870s to carry out social research. And also assume that Justice Bradley's dictum as to the disqualification of married women extended to their not being able to give consent for their own participation in a research project, so that consent instead would have to be sought from their husbands. How should the researcher handle such a disconnect between his own values, the values and norms of his own culture and society, and the values and norms of the culture and society that he wants to carry out his research?[53]

The best situation, of course, would be one in which the researcher manages to obtain both the consent of the husband as well as of the wife (although it would count for nothing in the context of the study culture). But even this, best of all possible worlds, assumes an ideal situation where the researcher is confident that

51. *Bradwell v State of Illinois*, 83 U.S. 130 (1872).
52. *Id.* at 141.
53. The ICH's Guideline entitled *Ethnic Factors in the Acceptability of Foreign Clinical Data E5(R1)* (1998) does not, despite what its title may suggest, concern ethical and social aspects of obtaining valid consent in foreign trials, but concerns itself almost entirely with potential (or alleged) differences in the pharmacological effect of drugs on different populations.

he understands the culture and its subtle social cues to be sure that the woman has freely given her consent. What if, for instance, the researcher is prevented by social convention from having an opportunity to interview the woman alone, without her husband (or parent, or village headman) being present? In such a situation, it may be well near impossible for the researcher to ascertain the true mind of the woman and therefore the validity of her consent (according to the researcher's values). Now, suppose it is known that the husband (or parent or village headman) objects: is it still open to the researcher to carry on with the study if there is a way to ascertain the free consent of the woman? What if such an attempt is regarded by both the law and public morality of that society as being deeply immoral and subversive to the established social order? Finally, consider one further situation: the prospective subject declines to make any decision on the matter, but simply says that she will leave the decision entirely to her husband (or parent or village headman) in whom she reposes absolute trust? In other words, what if a person has chosen of her own free will and autonomy to decide that another will decide for her?

Take another example. In Singapore, it appears to be a common experience for physicians to be told by very elderly patients that they do not wish to make any decisions regarding treatment choices, and to explain the situation and choices to their adult children, and to take their instructions entirely from these children. Before rushing to judgment on the last scenario, it is important to remember the earlier argument about non-delegation. In the case of the elderly Singaporeans, there appears to be a genuine exercise of autonomy in that these individuals (often with little formal education, compared to their very highly educated offspring) have absolute trust in their family rather than in their own understanding of what their physicians may want to tell them and in their own understanding of the choices. Is such delegation acceptable because it is ultimately based on trust and not coercion, as much as I may be entitled to rely on the advice of a trusted family solicitor? What then if a potential subject delegates his or her consent to participation in a trial on a similar basis?

The modern Western paradigm of personal autonomy makes many assumptions, not the least being that it *is* always possible for an adult person of sound mind to make most of the personal decisions affecting himself or herself. In many cultures, the paradigm of personal autonomy may not always hold true in all its aspects. Some of this may be due simply to cultural tradition and reflexes, but in the main simply because many people in less-developed countries do not have the resources to make independent decisions on their own. Nor may they want to. In many less-

developed countries with high rates of unemployment, many members of the family may not be engaged in the formal workforce, although they may carry out many economic activities at home that earn money for the family. In these societies, men are often the sole breadwinner and provider in monetary terms for the family. In the best of situations, the women may have to be content with a situation where their contribution is to the domestic life of the family, while the men in her family (her husband, father and brothers) have a social reciprocal obligation for her protection and economic subsistence. Her only safety net is her family. She cannot, if she disagrees with her family, leave it and find work and live on her own, because it may not be acceptable for a single woman to work and live on her own, even assuming that she can find independent employment. How can the consent of such a dependent person be judged, and in what terms, and on whose terms?

In economically better-off countries, appeals for participation in research is often based on altruism and return to society with monetary reward. In these societies, where universal medical care has given most people direct experience of the benefits of the medical technology which research seeks to advance, many people will voluntarily participate as a human subject for no remuneration, their reward being purely altruistic satisfaction.[54] Pure altruistic return is however a much more difficult argument to make in the context of a population where proper medical care is non-existent. In communities where life is a hard-scrabble day-to-day struggle for survival, it is at least understandable if not completely natural[55] for people to seek a return for participation as a human subject in clinical trials.

The difficulty is not only in how such bargains can be fairly struck, but also to properly control and record the true terms of the bargain, beyond the mere letter of the consent form. In societies where much economic life is transacted outside the formal economic system and letter of the law, potential subjects may have informal but nonetheless equally compelling expectations about the kind of benefits to be made available in return for their participation in the trial.

54. In Singapore, for instance, it is unlawful to offer to buy or sell blood (Human Organ Transplant Act, Section 14), so that the entire blood supply of the country is donated for free by volunteer blood donors. Technically, it would be unlawful for researchers to offer payment for samples of blood. The Singapore Bioethics Advisory Committee has strongly championed this principle of unpaid altruism in the context of human tissue banking and human tissue research – see its *Report on Human Tissue Research* (2002), at paragraphs 8.6 and 8.7, and 13.1.8 to 13.1.10. The Report in full text is *available at* http://www.bioethics-singapore.org.
55. And one might argue, completely ethical, particularly if the trial has an ultimately commercial objective.

In such situations, researchers may have to be sensitive to the possibility of such unvoiced expectations (if they are prepared to honour them, and if this can be lawfully and ethically carried out), for otherwise consent given on such expectations would be flawed. But it may also be that these expectations may not have been raised by the researchers themselves, but improperly by their local collaborators or agents in the field in their enthusiasm to "sell" the trial. So beyond merely recording consent, should there be independent mechanisms for eliciting feedback from research subjects on what they might have been led to expect, and independent checks to ensure that the expectations of the research subjects coincide with the terms of the formal consent that was given?

F. Consent, Risks, and Motivation

Finally, a word about the substance of disclosure. At least in Singapore, there is sometimes a temptation to take a very scientific approach and limit disclosure to matters of risks to the subject and obvious interests. But increasingly, there are many other considerations which are of interest and concern to subjects, beyond direct risks to themselves. Potential research subjects now not only want to know the risks they are being asked to assume, but also the *motivations* for the trial itself. Such motivations may include not only considerations such as the prospect of direct commercial gain, but also continued access to research and laboratory funding, the support of sponsors, academic prospects and reputation, access to publication in top-tier journals, and such. For many researchers, intangible considerations such as reputation may be the most powerful motivating factor of all, as demonstrated in the South Korean scandal surrounding Dr Hwang Woo-suk's fabrication of research data. Articles 4.8.1 – 4.8.15 of ICH-GCP E6 make for interesting reading, setting in detail what information must be communicated to potential subjects. There is naturally much on the risks and benefits of the proposed trial. But there is little or nothing about what needs to be disclosed about the motivations of the researcher, short of potential or actual conflicts of interests on the part of the researcher. In this respect, the corresponding provision of the Declaration of Helsinki[56] is hardly better.

The importance of the disclosure of motivations in contradistinction to risks may be especially important in societies where consent is given by subjects for reasons of altruism, and not for commercial gain. For a subject in an impoverished country who has agreed to enroll in a trial as a paid subject, information on the

56. Declaration of Helsinki, *supra* note 17 at ¶22.

motivations of the researchers may be less important than information on the risks. But for subjects who agree to participate out of a sense of altruism and public duty, information on the motivations of the researchers may rank more highly, and failure to disclose such motivations (which may have a direct impact on the subjects' altruism) may well vitiate the consent if it turns out that the subject concerned would not have participated in the trial had full disclosure of the motivations been made.

Disclosure of such motivations, honorable or otherwise, may become especially important in societies like Singapore, where life expectancies push well above eighty, in a country where everybody is only too aware of the limits of modern medicine, most people are keenly aware of the double-edged nature of advances in medical technology and are no longer prepared to take at face value a simple statement about "advancing medical knowledge."

Increasingly, people in economically better-off countries seem to be drawing a firm line between research for a public purpose and research for commercial ends. Even if there is no direct commercial gain involved, there is still the question of whether researchers should include in the consent disclosure information about motivations such as academic and institutional advancement, scholarly reputation, and access to funding. And if researchers should feel uncomfortable about including the mention of such things, then it may be that they have already answered the question as to whether motivations are relevant to consent, and whether they should be disclosed.

III. Conclusion

The purpose in raising all these points is not to advocate a politically correct approach by researchers embarking on trials in communities unfamiliar to them, for that way lies the worse errors of condescension and incomprehension. What is sought is merely an appreciation of the fact that cultural context matters, particularly in matters of consent, and an appreciation of the potential pitfalls when one culture deals with another on the basis of rules largely formulated on the social norms of one and not the other.