

ANNEX C

**WRITTEN RESPONSES RECEIVED DURING THE PUBLIC
CONSULTATION**

**Written Responses Received During the Public Consultation on
Ethics Guidelines for Human Biomedical Research**

Organisations / Institutions

- C1 Alice Lee Centre for Nursing Studies
- C2 Buddhist Fellowship
- C7 Cancer Science Institute of Singapore
- C8 Catholic Medical Guild of Singapore
- C12 Humanist Society (Singapore)
- C13 Lily-NUS Centre for Clinical Pharmacology
- C15 School of Public Health, National University of Singapore
- C16 SingHealth Tissue Repository
- C20 The Law Society of Singapore

Individuals

- C28 Mr Benjamin Gaw and Ms Keow Mei Yen
- C38 Member of the Public (1)
- C39 Member of the Public (2)

Comments from Alice Lee Centre for Nursing Studies

14 August 2012

Many thanks for the draft Ethics Guidelines for Human Biomedical Research.

We welcome the Guidelines and are very supportive to its recommendations. We believe this document will be a valuable resource for researchers in our department. We are pleased to see that an appeal mechanisms has been implemented for those who have proposals rejected. The variability in review process and opinion makes this a valuable inclusion.

We also noted the concerns raised regarding monetary coercion of participants. We support that every effort should be made to resist 'tempting' participation in research via monetary incentives (other than reasonable loss of time and costs).

Warmest regards

Professor Sally Chan
Professor and Head, Alice Lee Centre for Nursing Studies

Comments from Buddhist Fellowship

26 July 2012

A Buddhist's muse on the ethics of human biomedical research

That only constant in life is that it ever changes. Our parents' lives would seem rather different from ours, let alone life 2600 years ago. Human biomedical research did not exist back in the Buddha's time, but neither did most of the things we take for granted in our lives in the 21st century. The beauty of the Dhamma is its timelessness. This guide to leading a life with wisdom, love and compassion through right thoughts and right actions remain true and valid even as the context and nuance of life changes.

A lay Buddhist aspires to a life grounded in the 5 precepts.

- to refrain from killing and harming others, physically or mentally,
- to refrain from taking anything not belonging to us
- to refrain from sexual misconduct
- to refrain from false speech
- to refrain from intoxicating agents

Some of the ethical questions raised in human biomedical research include;

- Usage of foetal tissues and human embryos
- Genetic Intervention esp. gene therapy to alter our genetic makeup
- Human stem cell research
- Status of the human embryo

I will address these questions as a human being first, with full humility and recognition of my many own imperfections. I shall be guided by my understanding of the Buddha Dhamma. I shall also wear many caps; a doctor, a scientist, a father, a son and a husband, and a sick person to be; as I try to provide a humanistic answer. I cannot speak as the voice of the Buddhist community but as a member of the Buddhist Community. I would invite people to disagree with me, and to invoke the spirit of Ehipassiko. I shall frame my answers according to the moral and ethical questions that are commonly debated on.

Are we harming anyone?

Human beings begin life when a sperm fertilises an human egg cell. This results in a Zygote which has half its DNA from the father and the other half from the mother. The unicellular Zygote then gets implanted in a mother's womb and divides into a multi-cellular organism. It is called an embryo at this stage. These early cells are pleuri-potential, meaning that they can differentiate into different cells, for e.g. heart cells, blood cells, brain cells, skin cells, bone cells etc. At 5 weeks, the embryo's heart, brain and spinal cord starts to form but does not reach maturity until After 8 weeks, the embryo becomes a foetus. A foetus starts feeling pain around 20 weeks. By 26 weeks, most organs are fully formed but will continue to mature until the time of birth.

The million dollar question is when does life begin? Many people, including many Buddhists take that at the point of conception, i.e. when the Zygote is formed. This is point may make sense for those who believe in a permanent, unchanging soul.

I do not believe in a permanent self or soul. 'I' represent a consciousness or mental energy that resides within a brain that is supported by a physical body for its biological needs. This consciousness can only exist when there is a sufficiently mature brain which consists of brain cells, other neural tissues and nerve fibres.

Yes, I accept that a Zygote is 'alive' from conception but a person only comes into existence when there is a consciousness within the foetus, which is after 8 weeks gestation. However I do not know when that exact point is. With consciousness, there comes thought processes and thinking. Biologically, this occurs as electrical activity within the brain. Thus, there can be no consciousness without a brain. Our body is just a physical vehicle and our brain a mental vehicle during this life. Most doctors will accept that a brain dead person is just a physical body with no consciousness or mind.

Hence an embryo or an early foetus is not yet a human being. Using an embryo or early foetus for biomedical research is using human cells that have yet to mature to become a human being. Hence no human lives are sacrificed in this type of research. Sacrificing a late foetus for research is a different matter all together. By the time consciousness exists within a brain, that foetus has become a human being, a baby. However, I do not have the answer as to when the brain is sufficiently mature to accept a consciousness, and hence I am unable to precisely define what's early or late. 8 weeks gestation is definitely early whilst 26 weeks and beyond is definitely late but I do not know the cut off.

Cloning

Going by the concept that 'me' consist of a physical energy within a body together with mental energy (consciousness) within a brain, I have no firm objections towards cloning. Cloning will result in another being that is genetically identical to the 'cloned' creature. If ever a human being is cloned, he or she will be an exact genetic copy to the cloned person. However it is impossible to clone consciousness. The new person will look and maybe even sound the same as the cloned person. However his consciousness will be very different as a consciousness can only reside in one brain at a time.

Cross species genetic exchange

Currently a lot of research is going on, incorporating human genes into animal genes. The most important thing here is to have the right motivation for this research to be helpful to other humans and living beings in the future. Care is needed to prevent harm in these animals, especially in not creating animals with genetic features that are harmful to their life or causes pain to them. A line has to be drawn in genetic transfer going the other way from animals to humans. We do not know what kind of human beings will emerge if we try and incorporate animal DNA into humans. The potential for harm is very high and this is best avoided.

Playing God

The question of 'playing God' is probably viewed by most Buddhists very differently from adherents of the Abrahamic faiths. Buddhists reject the concept of fate or destiny in the conventional sense, i.e. that your life journey and outcome is already predetermined by an omnipotent creator and that you should just be grateful and be completely submissive to what has already been planned for you. Buddhists believe that many forces will mould our lives, and one of these powerful forces is our karma.

Karma to me is basically about cause and effect. For every action, there will be a reaction or consequence. Positive or negative, that would be dependent on our intent and the circumstances surrounding that action. Plant a mango seed and you get a mango tree. Yes, but only if you have planted it somewhere suitable, fertile soil, with readily available sunlight and water, and protected from people or animals trodding on it whilst young.

Every action, every movement, we are creating more karma to ripen in the future. In the current moment, our circumstances have been determined by what we have done in the past. Karma sets the scene but what happens next is also largely dependent on what we chose to do. As human beings, we always have a choice, albeit the choices available to us may be influenced by our past karma.

If we are taken ill, we have a choice to do the right things to get better or to allow ourselves to succumb to our illness. Even a simple sore throat, if not managed properly can sometimes lead to a serious pneumonia. If that is then not treated with the appropriate antibiotics and medical care, it is possible to die from that. So, we seek medical help when we fall sick. Break your leg, we will see a surgeon to fix it. That is common sense and that is what Buddhists are expected to do. We don't see it as a punishment from God and accept that the leg needs to remain broken, because that is our destiny.

And yet, with certain 'nasty' illnesses like Alzheimer's or Parkinson's come along, the attitude from many people can be very different. Because a cure does not yet exist although medications exist to help with symptom control and to slow the progression, some may take the attitude that it is your destiny or that this is a test from God. Gene therapy and stem cell therapy may one day convert these illnesses into chronic but well managed diseases and possibly even cure some affected patients. The concept that if we accept these treatments, we or the doctors are then playing God; is alien to most Buddhists.

After all, as Buddhists, are encouraged to 'play God' in our lives. We are always striving to improve our lives and lives of others around us. We are always striving to make this world a better place for all beings. We have the power to change things for the better, to reduce suffering for ourselves and others. We have the power to receive medical help if we are taken ill. Obviously, all these actions should always be tempered by being mindful that our actions do not harm ourselves and others.

For those who say that using Gene therapy or stem cell therapy, we are changing or modulating our genetic makeup, which is something that God has given us, and hence bringing on the playing God questioning. The question then is when are we allowed to play God and when are we not allowed to. If we get cancer, would seeking surgery or chemotherapy constitute playing God, especially since it is

now well recognised that most cancers occur as an interplay of our genetic susceptibility and environmental factors. Most people have vastly different thresholds on what constitute 'playing God'. Who then decides who is right and who is wrong? If you decides that treating a certain illness a certain way equates 'playing God', others should respect your decision to accept your illness as destiny and not seek medical help but it would be unjust for you to impose your beliefs on others.

Going back to Karma, I also believe that whilst getting a 'nasty' illness may be a manifestation of some of your negative karma; being born and living in a country with healthcare system that is able to provide the right treatment, and importantly as well, your own ability to fund the treatment or getting help from donations, should be seen as ripening of some of your positive karma to offset the negative karma. At the end of the day, one still has the choice whether or not to proceed with the treatment.

The question about what treatment the government should fund i.e. when and what to 'play God' with is a question on a different level that would be influenced by social, cultural, economic and political factors. Many karmic forces from many different people involved here!! We must not forget that in many undeveloped countries, millions of people are dying from 'simple' infections, dying from causes of death that we no longer see in our prosperous and developed country. Leave these people to their destiny? I say, we should 'play God' more and not less and help alleviate suffering in the world.

Bearing a child to facilitate gene therapy or stem cell therapy for an existing child

One hotly debated topic is that of parents conceiving and bearing another child with the hope that unborn child carries the 'good' gene to facilitate gene therapy to an existing child's 'bad' genes. Parents have always had their own agenda and motivation about starting a family and the number of children to have. Farming families may choose to have many children to ensure sufficient labour to work the fields later on. Not too long ago, when infant and childhood mortality is high due to disease, malnutrition and accidents, many parents chose to have as many children as possible to increase the chances that some of these children will survive into adulthood to look after them when they themselves grow old and frail. Some couple have children to save a marriage.

Who are we then to judge the motivations of parents who chose to have another child in order to save the life of a current child. Isn't their motivation about love and lessening the suffering of others. On whether this new child will be loved as much as the one saved, that is what everyone would hope for but will not be for us to decide. Karmic links may decide on this. Ultimately, for the new child, wouldn't it be wonderful that he or she was created to save another life?

Status of the human embryo

Many of the human embryos used in research as donated by couples on fertility treatment. These embryos a surplus to requirement and would be disposed off otherwise. Hence human embryos used for research are the ones 'saved' from destruction. At the same time these embryos are not yet

human beings albeit they having the potential to be one. Until these embryos develop fully into human beings, there is no reason to confer on them the same rights as human beings.

With metta,

Ho Eu Chin

26th July 2012

on behalf of Buddhist Fellowship

Angie Montford.

President

#848 10738

Comments from Cancer Science Institute of Singapore

2 August 2012

I have no major comments to this document except for the following:

Section 3.32 states that 'communication of clinically significant incidental findings to biological relatives should be encouraged....'. This concept is further reinforced in section 3.37, which states that 'participants should also have the opportunity to express their preferences about the sharing of such information with biological relatives.'

I am not sure why such a statement is required. Is it to facilitate disclosure of clinically significant incidental findings to family members in the event that the subject is deceased (particularly for genetic information)? For practical purpose, it should be noted that almost all informed consent documents do not have this provision for the patient to indicate whether to and who to share clinically significant incidental findings. How does the BAC expect the researchers to carry out this recommendation?

With regards to genetic information, from the medical point of view, it will be ideal that all affected family members of an index patient who is found with a genetic mutation be informed as they are at risk. However, it should be noted that in reality, this does not always happen for various reasons. I run a cancer genetics clinic and test patients for hereditary cancer syndromes. When a patient is found with a deleterious mutation, we strongly encourage the patient to share the information with siblings, who have 50% chance of carrying the same mutation. Not all patients are willing to share the information.

Similarly, not all cancer-free siblings are pleased to be told of the information (many would rather not know). If a cancer-free family member wants to know but the index patient refuses to share the information, the treating physician will be breaching patient confidentiality if he/she divulges the information, even if the information does benefit the family member. I am uncertain if the law will protect the physician if he chooses beneficence for the family member against respecting patient confidentiality. These are highly sensitive issues, and I am not sure that it is fair for a researcher to have to deal with communicating clinically significant incidental findings to family members, who did not directly participate in the research.

A more practical approach would be for the researcher to communicate the information to the patient, refer the patient to an appropriate clinical facility for further management, and stress that the information should be shared with family members – but the patient must be the one initiating the sharing, not the physician/researcher.

Regards,

Dr Lee Soo Chin
Cancer Science Institute of Singapore

Comments from Catholic Medical Guild of Singapore

15 August 2012



15th August 2012

Response to the Bioethics Advisory Committee's Ethical Guidelines for Human Biomedical Research by the Catholic Medical Guild of Singapore 15th August 2012

Dear Members of the BAC,

The Catholic Medical Guild of Singapore appreciates your efforts at presenting “an accessible and consolidated ethics resource” in the form of your latest guidelines for human biomedical research. However, we would like to make the following comments to further strengthen the guidelines in line with the BAC’s intent of improving the ethical standards of biomedical research in Singapore.

First of all, we think that **beneficence be included as one of the core principles of biomedical research.**

In sections 2.5 – 2.16, the guidelines has notably left out beneficence as a core principle, giving the reason that beneficence

“finds its main expression in medical treatment, deriving from the Hippocratic Oath. It expresses the first duty of the physician – to treat the patient. In research, however, the participants may not be patients, and even if they are, there is often no direct benefit for the patient from participation in the research.”

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it however goes on to concede that, “research is a process designed to yield a general contribution to knowledge, which is practically useful or theoretically important, and is therefore a public good”. Yet, the guidelines does not consider this the same as beneficence, opting instead to lump “the essential aspects of beneficence and non-maleficence” under the principle of “respect for persons”, which includes “respecting (individuals’) right to make their own decisions without being coerced, misled, or kept in ignorance, which the BAC refers to as autonomy”.

We think that the guidelines could be further strengthened here in two regards:



(1) The first is that while it is true that research participants are not patients and that they often do not “benefit” in the same sense that patients “benefit” from their therapeutic relationship with their doctors, it is not true that they do not benefit at all. Most research participants participate in research because of altruistic motives. By doing so, they do benefit from a sense of satisfaction and fulfillment in participating in something that may lead to the good of society in the future. This fact is not something that should be discounted. Furthermore, just because they do not benefit in the same way as patients do does not mean that the principle of beneficence should be taken away. Indeed, as the guidelines themselves suggest, biomedical research is in itself a “public good”. As such, even if not mentioned, the principle of beneficence is already foundational in every act of research because research is ultimately done for the benefit of other individuals in society. To remove beneficence as a principle of biomedical research is to remove the ultimate purpose of research all together.

(2) The second area that the guidelines might be improved upon concerns the co-opting of the principles of beneficence and autonomy within the single principle of respect for persons.

The principles of autonomy and beneficence are clear and distinct philosophical entities that have been described extensively by scholars and doctors all over the world.¹ While it is true that protecting the autonomy and rights of the individual are often good in itself, there are times when autonomy contradicts and conflicts with beneficence. For example, if a person states that he is suffering from a terminal illness and asks for a doctor to assist in his suicide, the principle of autonomy would support his “right” to die, whereas the principle of beneficence would protect the “good” of not ending his life prematurely. As such, while there is a need for a “respect for persons” and their autonomy, rights and interests, there must also be a co-guiding principle of beneficence to protect the good, welfare and safety of society and the individuals in it. It is thus a fallacy to lump them together.

As such, may we suggest that the principle of beneficence be included among the principles of biomedical research. Below is a suggested formulation of how the principle could be worded:

¹ Please refer to Tom Beauchamp and James Childress. *Principles of Biomedical Ethics*. New York, Oxford: OUP 2009 for a full treatment of the principles of autonomy and beneficence, in which it is shown that they are clearly different entities.



“Beneficence as a principle is concerned not only with the good of the individuals participating in research but more so, also involves the good of society as a whole. While it is true that research participants do not benefit from the goods of the therapeutic relationship in the same way that patients benefit from seeing a doctor for a medical condition, these participants often benefit from being able to contribute to the good of society. Through their altruistic participation, they often receive a sense of satisfaction and fulfillment, which results whenever someone participates in some public good. Most importantly, beneficence is the foundational principle of all biomedical research since all research, is ultimately aimed at achieving results that can be used for the good of others in society in the future.

Our second comment refers to the BAC’s examination of **the moral status of the human embryo**. In Sections 7.12 and 7.13, it states that

“The main controversial issue in embryonic stem cell research concerns the moral status of the human embryo, and arises from the fact that the human embryo is destroyed in the process of stem cell derivation. There is a wide spectrum of views concerning the human embryo. At one end, it is considered to be a human being from the time of fertilization, while at the other end, the view is that it is a mass of cells, no different from any other biological material used for research. After public consultation, the BAC adopted an intermediate position, whereby a human embryo is considered as having the status of a potential human being, but not the same status as a living child or adult. As a measure of respect and protection for the human embryo, the BAC recommended that human embryonic stem cell research, including the creation of human embryos specifically for research, should be allowed only when there is strong scientific merit in and potential medical benefit from such research. In addition, only embryos less than 14 days old should be used for the derivation of stem cells, as at around day 14, the primitive streak appears, signaling the onset of cell differentiation and development of organ systems, including the nervous system. As for the use of surplus embryos donated from fertility treatment by consenting parents, the BAC was of the view that rather than allow them to perish, their use in research would serve a greater good. This remains the BAC position on this issue.”

In doing so, we think that the BAC has tried to act moderately in a situation in which moderation cannot be applied. This is not a political decision in which one decides based on how many votes one has, nor is it a statistical decision in which one can give the mean

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or the mode as the final answer. This is a moral decision that needs careful thought and deliberation, and no unethical action should be allowed until the process has been carefully and completely debated.

The scientific literature is clear that human life begins from the moment of conception, or in the case of cloned embryos derived from somatic cell nuclear transfer, at the point where the nucleus has been incorporated into the enucleated ovum. We are of the opinion that, from this very beginning of life, “the human being is to be respected and treated as a person” and “from that same moment his rights as a person must be recognized, among which in the first place is the inviolable right of every innocent human being to life.”²

Thus, even if some should still question the moral status of the embryo, the fact remains that this view is not shared by those who consider the embryo as a distinct human entity that is fully deserving of human dignity and of a right to life.

In criminal law, if there is reasonable doubt that a person did not commit the crime, then the prosecution cannot convict that person. So long as there is reasonable doubt that the embryo may indeed be a human being, shouldn't the killing of these embryos be considered morally unacceptable until all doubt has been properly reviewed and removed? As such, **we do not condone the use and destruction of human embryos in biomedical research and call for an immediate moratorium on the use of human embryos in such research.**

Yours Sincerely,

Dr Colin Ong, Deputy Master

Dr John Hui, Immediate Past Master

The Catholic Medical Guild of Singapore

² Congregation for the Doctrine of the Faith, Instruction on Respect for Human Life in its Origin and on the Dignity of Procreation *Donum Vitae* (22 February 1987), I, No. 1: AAS 80 (1988), 79.

The Catholic Medical Guild of Singapore

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Comments from Humanist Society (Singapore)

13 August 2012

To: Bioethics Advisory Committee, Singapore

We, the Humanist Society (Singapore), a registered society representing the non-religious in Singapore, would like to express our support for the draft “Ethics Guidelines for Human Biomedical Research”.

We believe that research is vital to understanding nature and holds great potential for extending human lifespans and improving quality of life. In particular, we agree with the committee’s stand that stem cell research should not be prohibited, but instead regulated with guidelines based on our current understanding of Science.

Yours sincerely,

Humanist Society (Singapore)

Guided by reason, informed by evidence, driven by compassion

Comments from Lilly-NUS Centre for Clinical Pharmacology

16 and 21 August 2012

Greetings,

I am responding to the call for comments from the BAC on the proposed Draft Guidelines for Human Biomedical Research. Please allow me a short introduction. I am Dr Danny Soon, and currently the Managing Director of the Lilly-NUS Centre for Clinical Pharmacology, located at MD11 in NUS. We have been in operation for 14 years, and have conducted over 130 studies, in the field of clinical pharmacology research, including first-in-man, biopharmaceutics and experimental medicine studies. These studies are conducted in healthy volunteers, in the majority. According to HSA statistics, clinical pharmacology studies and Phase 1 studies, which overlap significantly, form 17% and 25% of all trials approved in 2011.

There is one clause that I would like to seek clarification from the BAC.

v. Compensation / payment to research participants. It has always been a fundamental principle that participation in research should be voluntary. There should be no coercion or undue influence on a prospective volunteer. In this connection, it is important to avoid financial inducement to participate in research. Participants may be reimbursed for legitimate expenses, such as the cost of transport and child care services, and actual loss of earnings. Reimbursement and any additional payment to be given, whether monetary or in kind, should not amount to an inducement. Donation of tissue for research, however, is considered an altruistic gift and there should be no payment of any kind, except in the case of donation of human eggs for research by healthy volunteers, as the process required to obtain the eggs is invasive and carries a health risk.

Participation in our studies is always entirely voluntary. However, it is common and customary, in Singapore and in other geographies where healthy volunteer studies are conducted, that research subjects are paid for their time on the study. The principle applied in formulating an appropriate payment quantum is predicated on a 'minimum wage' approach, sometimes known as the 'wage payment' model (*Dickert N, Grady C. N Engl J Med. 1999 Jul 15;341(3):198-203. What's the price of a research subject? Approaches to payment for research participation.*) In this model, a research subject is paid a pre-determined stipend, in accordance with the duration of his participation in the study. This payment is submitted to the Ethical Review Board for approval, and provided to the subject at the time of informed consent for entry into a study. It should be noted that such payments are fixed, and not based on reimbursement of the subject's expenses or loss of earnings. I seek clarification from the committee as to whether it is their intent to disallow such payments.

I do feel the BAC's position on this need to be clarified to researchers and IRBs. As to the question as to whether non-patient volunteer research in general will suffer impact if 'loss of time' payments were discontinued, I think the answer is self-evident. One needs to be circumspect when using terms such as 'vulnerable persons' and 'risky research'. It needs to be clear that the vast majority of healthy volunteer research subjects in our experience, are educated and with gainful employment. We have our own safeguards to prevent subjects from over-volunteering in Lilly studies, and if the concern is around a small minority of the economically disadvantaged who may look upon these payments as a major source of income, then for further protection, I have proposed in the past that some form of central tracking of non-patient research volunteers be administered by a coordinating body. Such a system already exists in the UK:

<<http://www.tops.org.uk/site/cms/contentChapterView.asp?chapter=1>>.

On the question of risk, it also needs to be clear to payment to volunteers are calculated mainly on the time spent on study, with degree of discomfort factored in if appropriate. There is no payment on the basis of 'risk' incurred. Further, any discussion of 'risk' is not complete without consideration of risk mitigation. In the phase 1 clinical protocols that are put forth to the IRB and HSA, a large measure of clinical monitoring is often in place. Also, not clinical pharmacology research is in novel therapeutics.

Last, I am quite concerned that there was not more of an effort to engage with stakeholders on this discussion. I was only made aware of the proposed changes when I chanced upon it in a press report, and a couple of investigators in other institutions I spoke with who conduct healthy volunteer research, were not aware of these proposals at all. I would urge a nuanced approach to this matter from the BAC.

Sincerely,

Dr Danny Soon
Managing Director & Principal Investigator
Lily-NUS Centre for Clinical Pharmacology, Singapore

Comments from School of Public Health, National University of Singapore

11 July 2012

I would like to reiterate the following points for BAC's consideration:

1. Para 1.10

The current definition of human biomedical research is very much disease focused and patient-centric. There is an increasing body of biomedical research that focuses on health seeking behaviour, knowledge, attitudes and practices of both patients and "normal" healthy individuals. In addition, clinical research requires "normal" subjects as a comparison group; etiological research using cohort studies starts with recruiting healthy subjects. A simple definition would encompass all research that involve human subjects/tissues/information with the aim of disease treatment, prevention and health promotion. I would like to propose that the following sentence be added the existing definition:

".....derived from humans or human tissues. Research on normal subjects and populations is also included in this definition."

1. Paras 4.7, 4.14

The proposed Personal Data Protection Bill recognises the role of "data intermediaries" or "Trusted Third Parties" (TTPs). TTPs are fairly common in many non-biomedical sectors but need to be "popularized" in the biomedical sectors. With an efficient and trustworthy TTP, data owners and research subjects can have greater confidence that their reversibly de-identified data are well protected. Propose adding a short para after 4.7:

"The use of 'data intermediaries' in the form of a 'Trusted Third Party' should be encouraged especially when data are kept in a reversibly de-identified form. Record linkages via TTP provide greater confidence to data owners and research participants that their data are adequately protected. Ideally for Singapore, either a single or a few large TTPs with the ability to conduct audits on the storage and use of reversibly de-identified data."

Happy to provide further clarifications if required.

Best regards

Professor Chia Kee Seng
Dean, School of Public Health

Comments from SingHealth Tissue Repository

13 August 2012

Background

- a. Incidental research findings (IF) are not limited to the disease area under study. A researcher looking into biomarkers for cancer may find that a sample of blood from a supposedly healthy volunteer actually shows hyperglycaemia whilst another researcher studying genetic predisposition for diabetes may instead discover that a patient sample shows *BRCA1* mutation, which carries a high risk of breast and ovarian cancers.
- b. High-throughput interrogation of alterations at the genomic level is now widely performed, using donated patient samples removed during surgery. These samples are banked in research tissue biobanks or repositories, of which the two largest collections reside in the NUHS Tissue Repository and the SingHealth Tissue Repository (STR).
- c. Tissue repositories ensure that samples are collected ethically and legally. Processed and annotated samples with de-identified patient information are then distributed to Principal Investigators (PIs) after approval by an oversight or tissue access committee.
- d. Despite its noble intentions, the proposal currently under consideration by the Singapore Bioethics Advisory Committee (BAC) relating to the return of IF¹ raises significant ethical and in particular, legal concerns.

BAC's existing recommendations

2.1 The BAC has previously recommended that tissue donations for use in research should be treated as outright gifts. As such, there is no obligation for researchers or tissue bankers to return research data nor should donors expect such benefits arising from the donation:

“Donations of tissue samples for use in research should be treated as outright gifts. Donors should not be paid any financial incentives for the donation..... As a corollary of this principle, donors should not expect any personal or direct benefit from the donation of tissue, including information of any medical condition or predisposition or likelihood of such discovered in the course of research on the sample. Likewise, researchers and tissue bankers should not be under any obligation to disclose such information to the donors, unless they

¹ “Where there is a possibility that the research may yield clinically significant incidental findings, participants should be allowed to decide whether or not to be informed of the result, prior to the commencement of the research. Participants should also have an opportunity to express their preferences about the sharing of such information with biological relatives, or others.” (para 3.37, proposed “Ethics guidelines for Human Biomedical Research, Singapore Bioethics Advisory Committee, 20 June 2012, pg.27)

have agreed to do so in advance of the donation.” (para 13.1.1.8, Consultation Paper: “Human Tissue Research”, Singapore Bioethics Advisory Committee, 27 Feb 2002)

2.2 The policies and SOPs of the STR have been formulated following these recommendations and we use a donation model for the acquisition of patient samples. It has been made clear to our donors that they will not receive any material benefits including any patient-specific data emerging from the research. The current proposal under consideration would be a complete deviation from the BAC's previous position and recommendations.

2.3 Nevertheless, I recognize that the position of the BAC might have shifted somewhat on this issue. In the subsequent publication on genetic testing, the BAC made a recommendation that appeared to run contrary to its previous guidelines as mentioned above:

"Human genetic research is not conducted with the aim of providing research participants with specific information about their genetic status or health. However, if there is a possibility that the research may yield individual data of clinical significance, the research participant should be informed of this possibility and whether he or she would receive such information if so desired, prior to participation in the research." (para 46, Genetic testing and genetic research, Singapore Bioethics Advisory Committee, Nov 2005, pg 7)

STR position: Return of research findings is not feasible

3.1 Return of research findings to donors is not feasible for the following reasons:

3.11 Unacceptable liabilities for biobanks. A large biobank like STR distributes up to thousands of samples a year to numerous researchers. A biobank has no means to monitor the research output of all these researchers and it is unlikely that PIs will allow the biobank access their research data. As tissue samples are donated to the biobank which subsequently distributes them, would the biobank be held jointly liable if a researcher fails to declare and return significant IF? The amount of data emanating from genomic research is colossal. Would the researcher/biobank be held liable if a significant IF has surfaced from the research but is not picked up by the PI who is studying a different question? The proposed policy will impose unacceptably high legal risks for the biobank and will threaten its very existence and the success of Singapore's biomedical initiative.

3.12 Danger of inaccurate data disclosure. A research laboratory is designed to uncover novel data and research assays are not conducted in a standardised manner as with an accredited service laboratory. The finding of a significant mutation may subsequently be found to be erroneous, giving rise to unnecessary distress and patient concerns. In extreme circumstances, the patient might have taken steps to distribute his properties and manage his financial affairs differently had he known that the research data were inaccurate. It will be crucial to emphasize that the IF is preliminary and needs to be confirmed in an accredited laboratory but it does not take away the distress and damage it might have caused in the interim. There is also the question as to who is financially liable for performing the confirmatory assays in an accredited laboratory.

3.13 Absolute need for anonymization which precludes follow-up studies. To protect patient confidentiality, biobanks de-identify or anonymize tissue samples.

- 3.14 Bioresources are only released to researchers after all identifiable patient information (ID) has been detached from the sample, which is then given a random code. In this process of **de-identification**, the biobank functions as the trusted third party who holds the link between the patient's identity and the code. This allows for valuable follow-up clinical data to be collected, de-identified and provided to the researcher whilst protecting patient confidentiality.
- 3.15 Alternatively, the link between the patient's ID and the sample code can be irreversibly destroyed in the process of **anonymization**. Obviously, this precludes the collection of crucial clinical information such as the response to chemotherapy and survival data.
- 3.16 Some biobanks will provide de-identified samples for researchers who require follow-up data but anonymize samples for studies that do not require such information.
- 3.17 If researchers and biobanks have an obligation to return IF, one possible consequence is that biobanks will completely anonymize all patient samples. This will render it impossible to return IF and thereby protect the researcher from legal liabilities, but will also impede important and valuable scientific research.
- 3.18 Patient autonomy and the need for genetic counselling. Some patients cannot handle the devastating news that they suffer from a mutation that will result in breast cancer or early dementia. For example, patients have jumped off buildings immediately after receiving news that they have HIV infection. Inheritance of a mutation like BRCA1 also has implications for family members and the donor will be burdened with the responsibility of disclosure to relatives who may be affected. A patient may well NOT wish to receive data relating to significant genetic alterations. For this reason, the BAC has emphasized the need for pre- and post-test counselling in the context of genetic testing². If return of IF is necessary, one would assume that the same requirements for genetic counselling will apply as part of the consent procedures:

"... When the tissue samples provided for clinical use are intended also for research, informed consent for the research is required in addition to the consent for taking the tissue for clinical use. Consent is also required if there is an intention to store the tissue for future use." (para 4.4, Genetic testing and genetic research, Singapore Bioethics Advisory Committee, Nov 2005)

"The individual should be given appropriate genetic counselling and informed about the nature of the test and risks of the procedure (if any) before giving consent. Pre-test counselling is thus intrinsic to the process of consent-taking." (para 4.6, Genetic testing and genetic research, Singapore Bioethics Advisory Committee, Nov 2005)

² "An individual tested positive for a predisposition to developing a specific genetic condition has to decide whether this risk should be disclosed to other family members who may also be at risk of developing the same condition. The individual may be additionally burdened with considerations for the family members who may or may not be affected by the condition and their wish to know or not to know. Family members who are not affected by the genetic condition may nevertheless be affected psychologically (such as the condition of "survivor guilt"). In view of these considerations, we emphasise the importance of pre- and post-test genetic counselling." (para 4.25, Genetic testing and genetic research, Singapore Bioethics Advisory Committee, Nov 2005, pg.30)

One implication of the need to return IF is that there will be a need for pre- and post-test genetic counselling and there are simply insufficient resources and trained genetic counsellors for that matter.

3.19 No consensus on what constitutes significant incidental findings. The range of possible genetic and biochemical alterations that may emerge from tissue-based research are legion. Yet, it is near impossible to define which are sufficiently significant and should trigger a return of IF. A genetic predisposition towards low sperm count may not be significant to an 80-year-old single male but may well be very significant to the scion of a wealthy family. Placing on the researcher/biobank the duty to decide which of the numerous genetic alterations (which will include not only mutations but polymorphisms) to report will pose far too onerous a liability and may stop all human genomic research in its tracks. For that matter, it is impossible to conduct any meaningful genetic counselling when the implications of the IF can range from bilateral ovarian cancers at the age of 40 to a polymorphism that may render one less likely to win a marathon race.

Concluding remarks

4. Return of incidental research data is a hotly debated issue with many angles that need to be considered and for that reason, there is currently no consensus in the research community. Whilst I fully appreciate the arguments to return significant incidental findings, the implications may well sound the death knell for biobanks and human tissue research.
5. I take the position that, for the moment, the earlier BAC recommendations of Feb 2002 should stand. Research tissue samples should be acquired as donations or absolute gifts and the act of donation be separated from the research intention³. Patient donors should not expect any material benefits in making the gift for the advancement of knowledge and the benefit of humankind in general. Similarly, biobanks and researchers should not have an obligation to return research results, incidental or otherwise to patient donors.

A/Prof Tan Soo Yong
Director, SingHealth Tissue Repository
Singapore Health Services

³ “Another way of simplifying consent is to have a system in which consent is completely delinked from the research purpose. In this system, the donor makes an absolute gift of tissue to a specified tissue bank. But it is made clear to the donor that the consent to the gift is not to be linked to or conditional upon any particular approved research use or purpose. It is also made clear to the donor that research applications are handled and approved by an independent ethics review committee or body...” (para 8.8-8.9, Human Tissue Research, Bioethics Advisory Committee, Feb 2002, pg.11)

Comments from The Law Society of Singapore

15 August 2012



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15 August 2012

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BY E-MAIL

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No. of pages: 8
(including this page)

Dear Mdm

**REQUEST FOR FEEDBACK ON THE BAC'S DRAFT ETHICS GUIDELINES
FOR HUMAN BIOMEDICAL RESEARCH**

We refer to your e-mail dated 13 July 2012 inviting the Law Society to provide its comments on the recommendations set out in the draft Ethics Guidelines entitled "Ethics Guidelines For Human Biomedical Research".

The Society appointed an ad hoc committee to review the draft Ethics Guidelines.

We are pleased to enclose our ad hoc committee's feedback on the matter for your consideration.

Thank you for giving the Society the opportunity to give our views on the matter.

Yours faithfully

Alvin Chen
Chief Legal Officer
Director, Representation and Law Reform

Enc.

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COMMENTS ON THE BIOETHICS ADVISORY COMMITTEE'S DRAFT ETHICS GUIDELINES ON HUMAN BIOMEDICAL RESEARCH

Introduction

1. We have been appointed by the Law Society of Singapore to provide our inputs on the Bioethics Advisory Committee's Ethics Guidelines for Human Biomedical Research ("BAC Guidelines").
2. The members of this ad hoc committee are involved in advising and representing individuals and organizations within the healthcare industry, as part of their legal practice. Some of the members also sit as members of Institutional Review Boards (IRBs) that review clinical research proposals.
3. We are of the view that the BAC Guidelines in general provide a good summary of the ethical, legal and social issues arising from research on human biology and behaviour and its applications and the policies on such issues.
4. We set out below our comments on the following specific issues dealt with in the BAC Guidelines:-
 - (a) Informed Consent from minors on turning 21
 - (b) Clinically significant incidental findings
 - (c) Human Tissue Research
 - (d) Compensation/Payment to Research Participants

Informed Consent from minors on turning 21

5. Paras. 3.22 – 3.25 of the BAC Guidelines refers to 21 years being the age of majority. This is correct. However, it should also be noted that with effect from 1 March 2009, Section 35 of the Civil Law Act now provides that a minor who has attained the age of 18 years is regarded under law as having sufficient capacity to enter into contracts (except for certain types of contracts such as contracts for sale/purchase of any land etc). With this amendment, a minor between the ages of 18 to 21 years can now purchase investment products or enter into commercial contracts as long as it is one of the transactions stipulated in Section 35 of the Civil Law Act. This amendment does not affect the Medicines (Clinical Trials) Regulations where the age for consent for participation in clinical trials is still stipulated to be 21 years. It would therefore appear that although the law now regards those aged 18 to 21 as being sufficiently mature to understand the implications of entering into various contracts where the young person may undertake fairly onerous legal obligations and commitments, the Medicines (Clinical Trials) Regulations still regards the age for consent for participation in clinical trials as being 21 years.

6. Human biomedical research does however, extend beyond just "Clinical Trials" as defined under the Medicines (Clinical Trials) Regulations. There are also non-drug studies where it may be desirable to recruit minors. In terms of what constitutes valid and effective consent to medical treatment, it has been generally accepted under common law that minors who are "Gillick competent" can consent for themselves, so long as they have sufficient understanding of the information being conveyed and are mature enough to appreciate the risks involved. We agree with the observation made in para 3.20 that research by contrast, is not generally designed to confer benefit on the research participant and there are thus usually no personal benefits against which to balance risk. This could make the decision whether to

participate, a more difficult one for the young person to make, but on the other hand there is no reason why the ability of the mature minor to consent to participation in human biomedical research, should be discounted entirely, particularly where the risks posed to the subjects are low. The fact that our law has now been amended to allow those aged 18 to 21 years to enter into certain contracts, further strengthens the case that in the area of low risk biomedical research, the mature minors deserve to be treated as competent decision makers exercising their right to autonomy.

7. The distinction between "consent" and "assent" as referred to in the BAC Guidelines is sometimes unclear. For example, para 3.26 requires the consent of the parents "in addition to consent from the child". Para 3.22 provides that "in clinical research which has a reasonable expectation of benefitting a child, the research might be allowed to proceed even without the child's assent, if the parents give consent but in general, the researchers should respect refusal from a child". We find it difficult to see the difference between "consent" and "assent" as used in these paragraphs. It is also unclear whether there is a positive obligation to obtain the assent of a child (as opposed to silence) and in the face of a child's refusal, whether the researcher is still permitted to proceed. This is important as the range of ages under consideration is wide and the guidelines presently are vague on whether there is a positive obligation to seek the assent of, for example, a 17 year old and whether the researcher can proceed in spite of refusal from the child (but with the consent of the parents). At what point would the child's distress stemming from his or her refusal, make it clear that proceeding against the child's objections would simply be against the child's best interests, which after all is always the paramount consideration for all decisions being made for the child.
8. Para 3.26 does however suggest that there is a positive obligation to obtain the child's consent. But again, it does not specify whether research can

proceed where the child objects. We are of the view that in the case of research presenting more than minimal risk, the child's objection should be allowed to stand (save perhaps in special situations of specific waiver by IRBs) and given such weight that it could even override parental consent as it could be against the child's best interests to be subjected to the research under those circumstances.

9. It is proposed under para 5.16(b) that once the minor reaches 21 year, his or her consent should be obtained for the continued use of the previously collected tissue or information related to this tissue specimen. If we recognize that the minor had already meaningfully consented to the use of tissue or information related to the tissue specimen between the ages of 18 and 21 years, such a requirement would be unnecessary. It is worth noting that under the Medical (Therapy, Education and Research) Act, anyone aged 18 years or above may give all or any part of her or his body for research or for therapy. Why then, would that minor of 18 years or above be unable to provide consent for use of tissue samples? In this regard, the need for a formal consent to be provided should be limited to instances where the minor did not give prior consent to the use of the tissue specimen or was below the age of 18 years at the time when he or she was included in the study.
10. Alternatively, at such time when consent or assent is being obtained from the minor between the age of 18 and 21 years, the minor may be requested to state in the consent/assent whether they wish to be consulted again on the continued use of their tissue specimen when they turn 21 years.
11. A similar point for consideration is whether a formal consent is required for the minor's continued participation in the clinical trial when the minor reaches 21 years. Again if we regarded the minor as being capable of giving meaningful consent when he or she agreed to join the study at between the

age of 18 and 21 years, then there is no logical reason why the subject needs to be re-consented at age 21.

Waiver of Consent

12. Para 3.27 provides for the waiver of the consent by IRBs for certain research done in the public interest. One of the conditions to be met before such waiver may be considered is that individuals who have indicated their wish to know will be informed in a timely manner of clinically significant findings, if reasonably possible (para 3.27(f)). It is likely that in situations where waiver of the consent requirement is being contemplated, there will be no opportunity for individuals to indicate their wish to know of clinically significant findings. In this context, it may be more appropriate to provide that all individuals will be informed of clinically significant findings in a timely manner, if reasonably possible.

Clinically significant incidental findings

13. In para 3.30, there is a proposal that research participants be given a choice whether to be informed about clinically significant findings. If they choose to be informed, then the researchers would ensure that research participants are informed and advised to seek medical attention and confirmation of the research result in a clinical laboratory. This suggests that should the research participant choose not to be informed of clinically significant findings, the researcher may not need to inform the participant. We feel that ideally participants should be notified of clinically significant findings (incidental or otherwise) that would impact on the participant's health or well-being regardless whether they had opted to be informed or not. This is particularly so because at the time when the participants made the original choice, they

may not have fully contemplated how such findings could impact them, and how they might value such knowledge particularly as they age.

14. As an alternative, perhaps the Patient Informed Consent should provide that unless the participant informs the PI in writing that they do not wish to be notified of clinically significant findings, the PI will notify the participant of such findings. In other words, all participants will be told of clinically significant incidental findings unless they inform the PI in writing that they do not wish to receive such information on such findings. The other exception would be in situations where the subjects have agreed to the anonymization of tissue samples, such that contributors cannot subsequently be traced.

Human Tissue Research

15. In para 5.13, it is provided that the donor may seek to limit the use of the human tissue and any information derived from the research. We know that some researchers obtain a general consent from participants for use of their human tissue for research in general, even without specifying what type of future research may be done. We are of the view that participants should be meaningfully consulted regarding the use of the tissue samples such that participants can choose whether they would permit such tissue samples to be used for research in general, or for research that is related to the particular area of research for which consent was originally sought. In other words, participants should be given a specific choice to decide on the ambit of the use permitted. There should be a separate section to allow participants to indicate their choice and it should not be an "all or nothing" consent that is tied to the original purpose of the research study.
16. Further, if the participant decides that they do not wish for their tissues to be used for further research, whether related to the particular research in question or not, it should be provided in the Patient Informed Consent that

such tissue samples should be destroyed by the researcher. It is observed that such a provision is not uncommonly omitted in Patient Informed Consent forms.

17. We are in agreement with para 5.44 on the issue of how to deal with legacy tissues. Researchers should be told clearly how best to deal with legacy tissues as there is often uncertainty amongst researchers as to whether consent is required for use of such legacy tissues for all forms of research.

Compensation/Payment to Research Participants

18. In para 3.5, there is a reference to payment to research participants and how such payments may amount to coercion. We acknowledge that care must be exercised so that any payments do not present as an inducement to research participants. It should also be noted that inducement may not come in the form of payment but in the form of subsidising cost of medical treatments that participants would otherwise have to bear should they not participate in the clinical trial. Often the point of contention is to get researchers to cover tests that are directly related to the research. It is not often that we encounter circumstances where participants are given substantial coverage for the entire medical treatment. If this should occur, it should be recognized as a potential inducement to subjects to participate in research.

Thank you for giving us an opportunity to provide our inputs on the BAC Guidelines.

Submitted by: Ms Rebecca Chew
Ms Mak Wei Munn
Ms Audrey Chiang
Ms Kuah Boon Theng

Comments from Mr Benjamin Gaw & Ms Keow Mei Yen

15 August 2012

S/No.	Para No.	Subject Matter	Comment
Consolidation of Reports			
1.	1.4	With the Guidelines, it is the intention of the BAC to render it unnecessary for readers to consult the various BAC reports.	<p>We agree that consolidation of BAC's previous Reports would be of great assistance to researchers and organisations as it would facilitate reference and adherence to the BAC Guidelines. However, given the need for brevity, there is concern that there may be certain important concepts or principles expressed in the earlier Reports which may not have been incorporated in these Guidelines.</p> <p>A sampling of what does not seem to have been incorporated in the Guidelines:</p> <p>(i) The portion on Genetic Testing in the Guidelines is covered in paras 6.1 to 6.13. However, the BAC report on Genetic Testing and Genetic Research ("BAC Genetic Testing Guidelines") spans 53 pages. Some content-specific items which appear very important in the BAC Genetic Testing Guidelines do not appear in the new Guidelines. These include: (i) a detailed explanation of what genetic testing is and what it can be used for (paragraphs 2.1 to 2.11); (ii) general and specific ethical considerations in genetic testing including the 20 recommendations given by the BAC with regards to how genetic testing should be conducted (paragraphs 4.1 to 4.80); and (iii) genetic counseling (paragraphs 4.81 to 4.89). The information set out in the Guidelines seem to provide a very broad summary of genetic testing and only appear to touch on the surface when it comes to content-specific information.</p> <p>(ii) The portion on Stem Cell research in the Guidelines is covered in paras 7.1 to 7.32. However the BAC Report on Human-Animal Combinations in Stem Cell Research ("BAC Stem Cell Research Guidelines") spans 34 pages. Similar to the BAC Genetic Testing Guidelines, the Guidelines does not include large portions of the BAC Stem Cell Research Guidelines. These include: (i) the detailed explanation on</p>

			<p>chimeras and hybrids as at out in paragraphs 2.1 to 2.15; (ii) the regulatory practices adopted by different countries set out at paragraphs 4.1 to 4.11; and (iii) the table of regulatory approaches adopted by different countries at pages 27 to 34 of the BAC Stem Cell Research Guidelines.</p> <p>(iii) Other omissions from the Guidelines include important principles such as the one stated in paragraph 8.7 of the Human Tissue Research Report “...<i>the governing common law principle that informs the letter of the law of both the Human Organ Transplant Act, and of the Medical (Treatment, Education and Research) Act: no person may enter into a contract for the sale of his body or any part thereof, including organs, tissue or blood. No person is under any compulsion to give. Nor is any person under an obligation to accept a gift...</i>”.</p> <p>Our view is that these background information can be very helpful in understanding the background and BAC’s thinking in relation to the relevant guidelines and recommendations. We therefore suggest that the Guidelines be expressed as being complementary to the previous Reports, and to also include references to the previous Reports, where helpful, within the Guidelines. This will also aid readers to navigate the BAC’s Reports.</p> <p>On another level, we also propose that there should be an effort in consolidating other relevant guidelines to human biomedical research. Particularly, we note that other than the BAC (which guidelines do not have the force of law), there are also a number of other guidelines issued by various bodies, including the Ministry of Health, the National Medical Ethics Committee, and the Singapore Medical Council. Whilst the guidelines issued by these bodies are presumably drafted with the specific target audience (such as the healthcare institutions licensed under the Private Hospitals and Medical Clinics Act (“PHMC Act”) in the case of the MOH guidelines), there may be a need to review and to consider whether there are any inconsistencies or ambiguities amongst these various guidelines, as a plethora of guidelines can lead to confusion as to the applicable ethical codes. In particular (see our comments to paragraph 1.10 below), there are some noted differences between the MOH guidelines and these Guidelines.</p>
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2.	1.10	Definition of “Human Biomedical Research”	<p>We note that the Guidelines have introduced a definition of “Human Biomedical Research” as follows: <i>“Human Biomedical Research refers to any research done for the ultimate purpose of studying, diagnosing, treating or preventing any disease, injury or disorder of the human mind or body, and which entails the involvement of humans, human tissues or information derived from humans or human tissue.”</i></p> <p>On the other hand, the Ministry of Health has defined “Human Biomedical Research” in paragraph 2.2 at pages 1 of 19 of the <i>Operational Guidelines for Institutional Review Boards (“MOH IRB Operational Guidelines”)</i> as <i>”any research on human subjects that involves:</i></p> <ul style="list-style-type: none"> <i>a. intervention on, interaction with, or observation of, humans;</i> <i>b. use or manipulation of any human biological derivative (e.g. human cells, tissues and body fluids), including those which were previously acquired and stored; and</i> <i>c. review, analysis and publication of previously compiled identifiable data for the purpose of studying, diagnosis, treating and/or preventing, any ailment, injury or adverse condition of the human mind or body.”</i> <p>From a quick comparison of the two definitions, it can be seen that the BAC definition is broader as it includes research on any form of information derived from humans or human tissues (whether identifiable information or de-identified information), whereas the definition in the MOH IRB Operational Guidelines appears to be limited only to identifiable data. Of course, the difference could be deliberate in that research using de-identified information derived from humans may be deemed less sensitive and thus should not fall within the MOH IRB Operational Guidelines. However, as noted above, it will be helpful if a study be undertaken to consider if some of these guidelines can be consolidated as well, to avoid creating any unnecessary or unwanted confusion.</p>
3.	1.17	Applicable statutes and subsidiary legislation	The BAC may wish to consider if there should be reference to the Human Organ Transplant Act.
4.	1.19	Relevant Guidelines	The BAC may wish to consider if there should be reference to MOH’s Licensing Terms and Conditions on Assisted Reproduction Services issued by the Director of Medical

			<p>Services on 26 April 2011 (“2011 AR Licensing Terms”). Section 9 of the 2011 AR Licensing Terms contain terms and conditions on the conduct of research, and Section 10 contains the conditions in relation to human-animal combinations.</p>
5.	1.22	Application of BAC Guidelines	<p>We note that the BAC Guidelines are intended to apply to research whether privately or publicly funded. We agree with the position taken by the BAC but are however concerned as to how the BAC Guidelines would in reality be implemented. Where research facilities are licensed under the PHMC, the application of the BAC Guidelines may be facilitated by way of a suitable licence condition under the BAC (although we are uncertain if there is indeed such blanket requirement currently). However, privately funded research laboratories (which do not carry out clinical services) would not fall to be regulated under the PHMC, and with the BAC Guidelines not having the force of law, there would be great concerns as to whether the BAC Guidelines would have sufficient reach to research carried out by privately-funded research laboratories.</p>
6.	2.7 to 2.20	BAC General Ethical Principles	<p>We note that the BAC has formulated the following five guiding principles:</p> <ul style="list-style-type: none"> (a) Respect for persons (b) Solidarity (c) Justice (d) Proportionality (e) Sustainability <p>We agree with the principles enunciated, but however, note that the principles governing human biomedical research as enunciated by the Ministry of Health although largely similar, are not identical to the BAC principles: See Section 3 of the MOH IRB Operational Guidelines, which specifically lists Beneficence as one of three fundamental principles.</p> <p>Again, such differences may lead to a possible conflict in implementation, particularly where the IRBs may be guided by principles which are differently articulated.</p> <p>In reality though, the ethical principles are not in and of themselves clear and distinct and each principle may embody concepts or shades of the other principles. Further, these</p>

			<p>principles would be distilled into specific guidelines, and there may be therefore be little or any difference in implementation.</p> <p>Nonetheless, as mentioned above, there may now be an increased need for a consolidated approach to regulating human biomedical research to ensure comity and consistency in approaches.</p>
Institutional Review Boards			
7.	2.45	Appeal Mechanism	<p>We agree with the setting up of an appeal mechanism. However, we suggest that the implementation of such appeal mechanisms not be the responsibility of the Institution (given that the IRB acts for and on behalf of the Institution). One important point of consideration in establishing an appeal process is the need to consider whether the decision of the IRB is akin to that of a public administrative body, and therefore subject to the principles of administrative law and public law.</p> <p>In any event, we suggest that, given that the IRBs are constituted pursuant to the directions of the MOH under the PHMC, any appeal against the decision of the IRB should be escalated beyond the Institution, and to the Director of Medical Services, who may be empowered to constitute a panel of experts to consider the appeal. The introduction of an elevated appeal process would be helpful to provide assurance that there is impartiality in the appeal process as it is easy for allegations of conflicts of interest if the Institution were to review the decision of the IRB (since the IRB acts for and on behalf of the Institution).</p>
8.	3 & 4	Roles and responsibilities of the Institutional Review Board (“IRB”)	<p>We also note that there appears to be increased roles and responsibilities placed on the IRB under these Guidelines.</p> <p>For example:</p> <p>(i) at paragraph 3.18, in the case of vulnerable persons not lacking capacity and when it is not possible for consent to be taken by an independent third party, the IRB may now give directions for consent to be taken by the researchers so long as there are provisions to manage the conflict of interest and sufficient safeguards to protect the welfare and interests of the participant.</p> <p>(ii) at paragraph 3.21, if the researcher is also the physician, the IRB may give</p>

			<p>directions for consent to be taken by the researcher as long as there are provisions to manage conflict of interest situations.</p> <p>(iii) at paragraph 3.26, IRBs should be able to waive parental consent in research that does not involve more than minimal risk.</p> <p>(iv) at paragraph 3.27, IRBs may consider a waiver of the consent requirement for research done in the public interest.</p> <p>(v) at paragraph 3.28, giving the IRBs the power in some cases to authorise research with regards to patients who are subject to the provisions of the Mental Capacity Act.</p> <p>(vi) at paragraph 3.47, giving the IRBs the ability the power to authorise research for valuable research involving recruitment of highly compromised patients who are unable to give consent and for whom no proxy is available to give consent.</p> <p>(vii) at paragraphs 4.12 and 4.18, the IRB is tasked to formulate formal procedures in consultation with the institution with regards to the release of medical records and other personal information.</p> <p>(viii) at paragraph 4.16, the IRB is tasked with the responsibility of considering the suitability of the extent and means of the de-identification of personal information in proportion to the risk posed.</p> <p>With the increased roles and responsibilities on the IRB, the onus on the Institutions would also increase to ensure that there is proper training provided for members of the IRBs. It may well then be that there is a greater need to have a properly defined appeals mechanism.</p>
			Consent Involving Children
9.	3.22	Consent v Assent	<p>We are generally not in favour of introducing a concept of either assent or consent of children below the age of majority.</p> <p>As noted under the Guidelines, “<i>in Singapore, there is no clear legal standing for assent as a procedure...</i>”. Such a procedure may therefore be confusing to a researcher who is tasked to obtain such assent. In the case of consent from children, it is similarly submitted that such a concept may not be that clear under Singapore law. Whilst common law recognises the concept of “Gillick” competency, there does not appear to</p>

			<p>be very clear guidelines for consent by minors for participation in clinical trials or research involving human subjects, since, as is noted in the BAC's general principles, there may not be actual benefit to the child in consenting to the trial, as opposed to consent for treatment.</p> <p>Further, Regulation 11 of the Medicines (Clinical Trials) Regulations (“Clinical Trials Regulations”) provides that that a person under the age of 21 shall not be a subject in a clinical trial unless consent is obtained from the subject's parent, guardian or legal representative. There is no corresponding requirement for consent (or assent) to be obtained for the trial.</p> <p>Whilst we do not advocate that consent or assent be a requirement, we agree that it is important that proper explanation be given to the child and that the IRB should ensure that such a requirement is set out in the protocol and the form of informed consent to provide that whilst ultimately it is the parent, guardian or legal representative who gives the consent, efforts should be made by the researcher to involve the child in the informed consent, but it should stop short of requiring consent or assent.</p>
10.	3.44 and 3.45	Consent from child in addition to consent from parent for research	<p>We also note that the BAC has recommended that for research on subjects below 21 years and involving more than minimal risks, such as those with invasive procedures, consent from parents should be obtained, in addition to consent from the child. However, for research on subjects below 21 years that does not involve more than minimum risk, the IRB should be able to waive parental consent. The Guidelines however are silent as to whether child consent is still required, and the implication may be that whilst the IRB may be able to waive the need for parental consent, the consent from the child may still be required.</p> <p>We also note that under paragraph 3.45, clinical research that has a reasonable expectation of benefiting a child might be allowed to proceed even without the child's consent, if the parents give consent.</p> <p>We have two suggestions:</p> <p>(a) First, we suggest that the Guidelines make clear that such waivers by the IRB in</p>

			<p>paragraph 3.44 can only apply in the case where the research is not regulated under the Clinical Trials Regulations. Otherwise, an anomaly may arise in a case where there may be a clinical trial which may not involve more than minimal risks (i.e. a non-invasive clinical trial), and IRB may waive a requirement for parental consent, which is required under Clinical Trials Regulations.</p> <p>(b) Secondly, on the assumption that consent of the child is a requirement in all research involving children (we have advocated above that there should not be such a requirement), we suggest that it should be the consent of the child that is waivable, rather than parental consent. Otherwise, there may an inadvertent displacement of the authority of the parent over the child, where the child may agree to participate, but where the parent may not. For example, it is likely that a parent would still need to be involved in the child’s participation in the research (such as arranging for the parent to be present for the research or tests to be carried out, etc). The parent’s wishes should be respected in such a case. This position would also be consistent with the position articulated in paragraph 3.45 and therefore does not run the risk of creating many different layer of consents (for invasive research, for non-invasive research, and for clinical research).</p> <p>As important as it is to take into consideration the views of the minor who will be subject to the research, an approach requiring both consent from the minor and parent may pose a potential problem in situations where the parent consents to the research and the minor does not.</p> <p>In the event of a deadlock, would the parents’ decision trump that of the minor, and if so, what purpose would there be in having both the minor and parent give consent to the research?</p>
Use of Personal Information			
11.	4.12, 4.13 and 4.18	Use of Medical Records for Research	We note that the BAC has recommended that appropriate access be given to suitably qualified professionals for the purpose of research. We note that the BAC Guidelines are silent on whether there is a need to obtain consent from patients before the release of

			such medical information. Whilst the BAC does advocate that the Healthcare Institutions and the IRBs formulate clear procedures for the release of such medical records and other personal information, we suggest that the Guidelines should make clear that all such access must be subject to IRB approval (similar to the need to obtain IRB approvals for other forms of research and which would be in line with paragraph 4.15 of the Guidelines).
Tissue Banking			
12.	5.8	Guidelines on Human Tissue Research	<p>We note that the Guidelines provide that all research involving human tissue, whether identified or de-identified, should be reviewed by an IRB and approved before it commences.</p> <p>At present, we understand that tissue banks are required to be licensed under the PHMC Act. We note that under the Guidelines for Healthcare Institutions promulgated pursuant to Regulation 4 of the Private Hospitals and Medical Clinics Regulations (“PHMC Regulations”), the term “Tissue Banking” is defined as “<i>the activities of donor screening, procurement, processing, storage and distribution of human tissue intended for transplantation into a human</i>”. The term “tissue bank” or “tissue banking” does not appear to be defined in the PHMC Act or the PHMC Regulations. Accordingly, it is not clear if it is only tissue banks that deal with organs for transplantation (and not tissue banks in general (or biobanks for that matter)) that would need to be regulated under the PHMC Act.</p> <p>The question thus arises as to whether a private tissue bank dealing with tissue banking only for purposes of research and not for transplantation would necessarily fall within the jurisdiction or purview of a hospital’s IRB. If it does not, then the requirement that all research involving human tissue be approved by an IRB may be hard to be implemented in practice.</p>
13.	5.41	Imported Tissue	We also note that the Guidelines require researchers to obtain written assurance from the source authority when dealing with imported human samples that the samples have been ethically and legally obtained, and that the test of ethical acceptability would seemingly be the Singapore ethical standards. We suggest that this requirement be removed. We understand that typically, tissue imported from overseas laboratories and institutions are

			<p>usually done by way of Material Transfer Agreements, and such samples are usually provided on an “AS IS, WHERE IS” basis. Accordingly, it would be an uphill task to require these overseas laboratories to provide written assurance of any form that the samples have been ethically obtained according to their ethical standards. Furthermore, it appears that the applicable ethical standards are that of Singapore. Given that these are foreign laboratories, it is hard to conceive that the foreign laboratories would be prepared to give any such assurances at all.</p>
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Comments from member of the public (1)

27 July 2012

From the press report and brief look at the provisions related to children, I am deeply concerned about the waiver for consent for persons under 21 years if the risk equates with minimal risk. I think this is far too lax a standard.

(1) The concept of “minimal risk” is poorly defined in current ethical guidelines in Singapore, and elsewhere. More importantly, empirical research has indicated that leaving the matter to IRB “judgment” is simply to invite significant variation of interpretation of what amounts to minimal risk. The indications in the proposed guidelines are simply insufficient considering the potential gravity of the issues involved.

(2) Secondly, parental consent is not relevant simply because of various risks involved in the research, but also out of basic respect for parental responsibility and the implications participation might have on the child’s daily routines and so forth. None of this seems to be appreciated by para. 3.26 and I fear that it may open the door to unwise waivers. One possible additional caveat to the waiver should be that the research could not reasonably be undertaken if parental consent were insisted upon, and this would be detrimental to the public health interest or the general public interest. I understand that this is already the view taken by some local IRBs.

(3) In short, more detailed guidelines are necessary on such an important issue as waiver of parental consent, which the law considers as a first line of defence in protection of a child’s interests.

Finally, I have written in some detail on these issues in the context of minors and biomedical research. I attach these articles if they have not already been referred to, and might be of some use to the BAC. The relevant portions in the Singapore Academy of Law Journal article are 44- 50.

Comments from member of the public (2)

21 and 29 July 2012

Summary of Main Revisions

"The BAC recognises this importance and is of the view that research institutions have a responsibility to ensure that the requirements of research integrity are observed. The BAC has recommended that there be an appeal mechanism, to allow the Principal Investigator to make an appeal for reconsideration of their proposals if they are not approved by an IRB. Institutions would be responsible for ensuring that such a mechanism is in place."

Question: Drawing along the same parallels, property agents in Singapore used to be unlicensed and if they misconduct themselves, it is up to the companies to decide their own disciplinary action. Sometimes, these companies mete out different standards of punishment such as dismissal, suspension or a written warning letter. In addition, the so-called 'disciplinary committee' usually consist of a more senior staff who will have the unfettered sole decision to do what he/she prefers while the rest will usually be the silent majority.

After several complaints from members of public, a new statutory board Council for Estate Agencies was set up to hear grievances and allow them to investigate complaints while at the same time, help be a bridge of communication and to increase public trust between consumers and property agents.

They also help to standardise the system by having a demerit point systems for each property agent so that the process will be clear and transparent.

IRBs in Singapore usually consist of members who have full time day jobs. Quite a lot of them may not have enough training or time to fully assess the merits of each projects.

Research institutions are may not be truly capable of having a good IRB in place. Having a centralised IRB with full time staff with adequate training allows more transparency and accountability while at the same time, maps out the common similarities between researchers and research participants. Moreover, it disallows researchers and PIs from shopping around any research institution in Singapore.

For example, HSA Singapore already regulates and enforces clinical trials in Singapore and metes out punitive action to manufacturers or importers of poorly made medical devices or harmful pharmaceuticals. In UK, HRA Health Research Authority was set up in 2011 Dec to look into this issue.

HRA UK allows the blowing of whistle from research participants but at the same time, it helps gather patient advocacy groups as a one-stop service so that research institutions can forward to having a more cohesive adequately informed patient advocacy groups rather than having to hunt or source for research participants.

May I know if there is a consideration along this line?

In your ethical guidelines that "3.17 In such cases, consent should be taken by independent third parties, whenever possible, and prospective participants reassured that they have nothing to fear in declining research participation or in contributing tissue for research."

My working place needs many research participants who serve as control groups. As a result, many researchers need to 'advertise' around and ask if their friends, families or spouses are willing to donate their time for research purposes. Many fear reprisals. Even when there was an assurance that it is not true, there were rumours that it could turn up in other ways such as a delay in promotion, or lower bonuses or getting marked down or denied opportunities later.

In reality, it is quite difficult to even get independent third parties. Presently, many researchers already have difficulties to get people to be the controls for their research. To get independent third parties will be an additional obstacle. It is necessary but in reality, it will be hard to implement on the ground level.

In addition, many researchers are not even familiar with the various Acts and ethical guidelines proposed by BAC. Especially for visiting investigators, genuine safety lapses may occur as they may not be well-versed in the guidelines. Unless they are forced to attend some courses in this area, it is likely that they may not know what the boundaries are until they are scrutinised by their IRBs or have infringed the guidelines.

Having a one-stop centre may help solve this problem. This one-stop centre could oversee all the research institutions. This one-stop centre could help to disseminate information to researchers and research participants and form a bridge of understanding while at the same time, enforce the guidelines in the research. All guidelines or Acts will not achieve its full effect if there is no concerted effort to implement or enforce it through a single body.

In addition, this one-stop centre could be the independent third parties. Many research participants are scattered all over and a researcher will usually have difficulty finding suitable candidates.

For example, the CHIP trial in 2008- (<http://www.chip.sg/>) "CHloroquine for Influenza Prevention" - is a new drug trial in which chloroquine, a simple and well-known medicine, might prevent flu. It was advertised widely in the press which costs more than S\$10K to have a coverage in Straits Times. This money could have been saved if there was a one-stop centre to help disseminate the information through their established network.
