RESPONSES TO THE CONSULTATION PAPER "ADVANCING THE FRAMEWORK OF ETHICS GOVERNANCE FOR HUMAN RESEARCH"

The Consultation Paper "Advancing the Framework of Ethics Governance for Human Research" was sent to 37 parties, and 19 responses were received.

Written Responses:

1. Alexandra Hospital (Private Communication)
2. Defence Medical & Environmental Research Institute
3. Faculty of Medicine, National University of Singapore
4. National Cancer Centre
5. National Dental Centre
6. National Healthcare Group
7. National Heart Centre
8. National University Hospital
9. Parkway Group Healthcare
10. Raffles Hospital
11. Singapore General Hospital
12. Singapore Tissue Network

Email Responses:

1. Bioprocessing Technology Centre
2. Genome Institute of Singapore
3. Institute of Mental Health/ Woodbridge Hospital
4. Institute of Molecular and Cell Biology
5. KK Women's and Children's Hospital
6. National Medical Ethics Committee
7. National Skin Centre

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Website: http://www.dso.org.sg

6 October 2003

A/Prof Terry Kaan,
Chairman,
Human Genetics Subcomittee,
Bioethics Advisory Committee,
10, Science Park Road,
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Singapore Science Park 2
Singapore, 117684

Dear Terry,

Feedback on BAC Consultation paper Entitled "ADVANCING THE FRAMEWORK OF ETHICS GOVERNANCE FOR HUMAN FOR HUMAN RESEARCH."
(Ref: BAC letter dated 15 Sep 2003)

I refer to your letter above. Pardon me for the one week delay in reply but your letter was received when I was on overseas duties. Since returning my Institute had been incorporated into the DSO National Laboratories, we merged with a sister centre to form the new DMERI@DSO and moved to a new building at the Kent Ridge Medical Campus.

You may like to know

- That MINDEF has adopted the National Medical Ethics Committee (NMEC) Guidelines in formulating policies and procedures governing Research involving Human Subjects since 2000. On consultation and advice from the NMEC chaired by Dr Chew Chin Hin and from MOH, the Armed Forces Council (AFC) approved the implementation of these guidelines on the 25 Oct 1999. The Armed Forces Council is the highest decision making body for the Singapore Armed Forces and MINDEF and is chaired by the Minister of Defence.

- DMRI, which is MINDEF's human science research institution implemented the decision and set up its IRB called the DMRI Research Ethics Committee in Jan 2000.

- Regarding Para 3.8 of your draft, the same AFC had set the overall direction by which, under defence and security considerations, abbreviation, waiver or temporary suspension of the ethics procedures and requirements is made.

Because we had largely implemented the NMEC guidelines and having read the BAC draft, I can support the 8 recommendations and have no further comments to add.

HOWEVER I would like to point out that I am giving my feedback entirely as the Director of the Institute as the letter intended. These views do not represent the official feedback from the Ministry of Defence. Should the BAC desire to solicit the official view of the ministry, you are advised to right to the "Permanent Secretary, MINDEF."

I hope the above feedback is useful to you.

Yours Truly,

BG(ret) A/Prof Lionel Lee
Director, DMERI@DSO

Copy to

CEO, DSO

Faculty of Medicine
Dean's Office

NUS National University of Singapore

Professor John Wong
Dean
Faculty of Medicine

20 October 2003

Associate Professor Terry Kaan
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Dear Terry

REQUEST FOR FEEDBACK ON BAC CONSULTATION PAPER ENTITLED "ADVANCING THE FRAMEWORK OF ETHICS GOVERNANCE FOR HUMAN RESEARCH"

Thank you for asking for the Faculty of Medicine's input on this paper.

We are unanimous that this is an excellent step forward and most timely.

There were 3 comments which I would like to share with you, namely:

(i) The commitment required for IRBs to be effective. Staff feel that hospitals need to be told that staff involved in IRB work should have this regarded as part of their job description, that is a part or all of a full-time equivalent (FTE) of a Senior Clinician.

(ii) Some staff raised the issue regarding monitoring of the hospital IRBs to determine their effectiveness and ability to monitor and enforce research standards.

(iii) Staff were uncomfortable about utilizing a commercial IRB because of potential conflicts of interest or because of inability to have these reflect institutional policy and standards.

Thank you.

With kindest regards,

Yours sincerely

John

Professor John Wong
Dean
Faculty of Medicine

JW/rf

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22 September 2003

Associate Professor Terry Kaan
Chairman
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Singapore 117684

Dear Professor Kaan,

Response to BAC Consultation Paper: 'Advancing the framework of ethics governance for human research'

Thank you for inviting the views of Professor Soo Khee Chee and others of the National Cancer Centre on this excellent consultation paper which clearly demonstrates deep understanding of the increased complexity of current biomedical research and advances thoughtful recommendations for an enlarged national framework to serve the interests of both the research fraternity and society at large.

I appreciate the opportunity to offer my personal views below. These are mine alone and do not necessarily reflect those of my colleagues or the National Cancer Centre. For ease of reference, I shall present my responses by page and section of the BAC Consultation Paper.

Section 2.13 (page 9)

Greater importance needs to be attached to the level of understanding that human research subjects attain during informed consent procedures. We need to move beyond acquiring the external façade of seeking and obtaining informed consent. Substantially more attention ought to be paid to assessing the comprehension of research subjects and to developing and implementing culturally appropriate informed consent processes.

Section 2.23 (page 11)

Directives to streamline ethics reviews (especially of pharmaceutical trials) must never lead, directly or indirectly, to any compromise of standards.

Recommendation 1 (page 16) and Section 3.6 (page 18)

The term 'human subjects' should be understood to encompass research involving use of any human biological material (tissues, blood and derivative products,

cells and body fluids), clinical, research and disease databases, data from imaging studies in addition to face-to-face encounters with patient subjects.

Section 4.19 (pages 23 - 24), Section 5.27.1 (page 31), Sections 5.30 & 5.32 (page 32)

It is my view that major obstacles to high ethical integrity are powerful and pervasive self interests of career advancement (for individual investigators) and financial incentives (for host institutions and industry). IRBs can become vulnerable to peer, institutional and administrative pressures to be non-probing and to grant the imprimatur of ethics approval with least delay. Unless IRB members feel assured that truly independent actions and decisions will not attract personal disadvantage (particularly for those who are themselves in the employ of the institution), the possibility that some ethics decisions may be self-serving is difficult to dispel. The BAC is undoubtedly cognizant of high capitation fees that pharmaceutical companies offer for enrolment of human subjects and the invidious use of clinical trials as a marketing tool.

Human subjects who are approached for voluntary enrolment in clinical studies should be informed of financial arrangements offered by corporate sponsors (typically of drug trials) to the trial investigators and their institutions, together with an explanation of how such fees are justified.

Section 5.15.3 (page 28)

The rationale for evaluating actual versus anticipated outcome or results is unclear *vis-à-vis* bioethics.

Section 5.16.1 (page 28) and Section 5.18 (page 29)

While it is axiomatic that 'bad science is bad ethics', it is nonetheless my view that IRBs should not be encouraged to undertake in-depth expert scientific assessments of research proposals. In fact, they should be actively discouraged from doing so. There are at least two reasons why scientific review by IRBs is undesirable and could easily undermine the quality of research ethics. First, IRBs are optimally comprised of a significant proportion of non-scientific and non-medical lay members. Second, medical and scientific members of IRBs may not easily dissociate their professional interest in research from the accompanying ethical issues. The unintended failure of an IRB member to distinguish between his role as ethics overseer from his professional interest in promoting research (i.e. 'good science may not be good ethics') is unhelpful in achieving consistently high standards of bioethics. This may be compounded within relatively small specialty groups whose members often find themselves sitting in judgement over each other's research proposals.

Section 5.20 (page 30)

I applaud and commend the Consultation Paper for recommending that IRBs receiving much higher standing and support than they currently receive. It needs to be equally recognised that appointment to IRBs must be preceded by training to serve competently as IRB members i.e. it is insufficient merely to appoint well-intentioned individuals in good standing with the community. National standards of IRB performance could be helpful in developing greater uniformity of scrutiny, failing which investigators may resort to 'ethics shopping' if some IRBs are known to have a record of greater laxity than others.

The performance standards of IRBs ought to be monitored e.g. time taken to render decisions, number of face-to-face meetings, active and inactive IRB members,

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frequency of dissenting opinions (if any), frequency of queries directed to investigators and proportion of approved versus unapproved applications.

Notwithstanding the considerable difficulty in recruiting conscientious members to serve on IRBs, each member's term of office should be limited to 2 – 3 years. Prolonged IRB membership without prospect of termination usually leads to decreasing participation and loss of rigour.

The Consultation Paper correctly recommends that additional IRBs be established if the workload justifies. It will be helpful to provide some guideline on what level of work should trigger an additional IRB e.g. number of applications per year, hours expended per year.

Section 5.27.3 (page 31)

External and lay representation on IRBs should be mandatory rather than optional.

Sections 5.49 – 5.50 (page 36) and Section 6.10 (page 41)

A lay summary of research proposals could be useful and required for submission to IRBs. However, it would be unwise and possibly risky not to provide IRBs also with the scientific research proposal (i.e. the proposal submitted for funding). Approved and funded projects will implement the experimental or study design detailed in the scientific proposal - details that may be absent in a separate description of the same project submitted for ethics review. Such omissions will not be apparent to the IRB if it does not also receive the scientific proposal. A possible consequence of this is ethics approval on the basis of incomplete information.

In order not to impose burdensome requirements on investigators, the lay summary could be brief and concise setting out salient features e.g. study objectives and rationale, experimental design, definition of study population/materials, data analytical methods, ethical considerations relevant to the proposed study and measures implemented by investigators to address ethical issues.

Sections 6.37 & 6.39 (pages 46 - 47)

Careful consideration should be given to allowing researchers (whether medically trained or not) access to medical records. In theory, non-medically trained research personnel could be entrusted to maintain confidentiality. In practice, there may not be sufficient general awareness among research personnel of the responsibilities that attend privileged access to personal information. The requirement for researchers to provide a signed undertaking to respect confidentiality of medical information on every occasion that clinical records are accessed may help to address this concern.

Harmonising ethics and scientific reviews

A significant proportion of the present workload of IRBs relates to the requirement of both the National Medical Research Council (NMRC) and Biomedical Research Council (BMRC) that research proposals must have prior ethics approval before scientific review to determine funding. In recent years, NMRC and BMRC have announced deadlines for submission of proposals that give institutions such as the National Cancer Centre only about one month to complete internal reviews (assuming investigators have pre-written their proposals much in advance) and to obtain ethics approval. These timelines are quite unrealistic if we aspire to high quality research and ethics. On the ethics front, it has resulted in extremely hurried reviews that, in my view, do not pass muster if we are sincere about upholding high standards of bioethics.

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Two alternatives are clearly preferable. The better option is to reduce unnecessary work now imposed on IRBs by seeking ethics reviews only of proposals that have successfully secured funding. This should substantially reduce the work of already overextended IRBs because the scientific review culls many proposals. An obvious disadvantage is the perceived additional delay incurred if scientific and ethics reviews proceed in sequence. The second option therefore might be to consider simultaneous reviews. Since scientific reviews typically take several months to complete, this same period could be used for more thorough and meaningful ethics review without incurring any additional disadvantage to investigators. If the present system of rushed IRB reviews is not rectified, one fears that ethics reviews will be merely an instrument for conferring a shallow patina of respectability to human research.

I should like to reiterate my personal appreciation to the BAC for its thoroughgoing approach and the opportunity to provide feedback.

Yours sincerely,

OL Kon

Copy: Director, National Cancer Centre

National Dental Centre (NDC) – Summarised Response

Paragraph 2.1
Amended as:
"In the main, such advances in biomedical knowledge have been beneficial, and research *"has been" (added)* conducted in good faith for the benefit of humankind."

Footnote 2
Amended as:
"Declaration of Helsinki on Ethical Principles for Medical Research Involving Human Subjects adopted by the 18th World Medical Association General Assembly in Helsinki, Finland, in June 1964 and *"more recently amended" (amended)* at the 52nd World Medical Association General Assembly in Edinburgh, Scotland, in October 2000."

Paragraph 2.13
Amended as:
"... researchers are under a duty to give full explanation and information of (among others) the objectives *"and risks" (added)* of the proposed drug trial."

Paragraph 3.6
The definition statement is too long. Could be improved. How about:
"Clinical research refers to any research study, trial or activity involving human subjects, human tissue or use of medical / genetic information of identifiable or anonymous individuals. These are undertaken with a view to generate data about the medical, genetic or biological processes in human physiology or diseased states; to determine the safety, efficacy, effect or function of any drug device; and diagnostic, surgical or therapeutic (whether invasive , observational or otherwise) procedure in human subjects.It has the potential to affect the safety, health, welfare, dignity or privacy of the human subjects involved in the study, or of the donors of human tissue or of the family members of any of the human subjects or donors thereof."

Paragraph 4.5
Amended as:
"...most forms of biomedical human research *"may" (added)* unavoidably involve some degree of risk of harm (however minimal or remote) to the human subject."

Paragraph 4.6
Amended as:
"Ethical assessment and judgment therefore necessarily involves an assessment and *"weighing" (added)* of the potential harms and benefits."

Paragraph 4.13
Amended as:
"It is desirable that a "common" (added) code of applicable principles for ethical governance be eventually formulated for the *"common" (deleted)* guidance alike of ethics committees, institutional review boards, research institutions, researchers, *"the*

human subjects of research" (deleted) and all other parties involved in human research..."

Recommendation 3
The word "institution" here is not limited to a medical/dental institution? May include a research laboratory?

Section on "Shared, "Domain" and Other Special Institutional Review Boards"
In this section, the proposal of a 'shared IRB' may not be practical. It may be possible to share an IRB secretariat but not an IRB. Even then there may be logistics problems. Does the specialist IRB or domain IRB refer to a scientific review panel/board? These two terms may add to confusion.

Paragraph 5.15.1
Amended as:
"... before the proposed research *"can" (amended)* be carried out. In the majority of developed countries, this is made a statutory or otherwise legal requirement."

Paragraph 5.40
"On reviewing the proposal, the proposed lead IRB may then decide to accept nomination as the lead IRB, and if not, to give reasons why other IRBs may be more appropriate... If the proposal is accepted by the proposed lead IRB, the first application for review should be made to that lead IRB."
This is not necessary as it adds to paper work and increases time taken for the processing of the applications. The researcher would have decided which IRB would be the lead IRB to apply to.

Paragraph 5.43 (first bullet point)
This statement suggests that the research is simultaneously assessed by variable IRBs. Better to standardize SOPs inclusive of standard criteria for reviewing protocols, etc. The lead IRB approves and this approval can then be submitted to other respective IRBs which can then 'cross-recognise' the approval, expediate the application process with or without minor modifications. If the application is submitted to various IRBs at same time, the researchers may get conflicting feedback from the IRBs. For such projects, the scientific merit should be done by the CTCC or its equivalent for non-drug trials?

Paragraph 5.57
Amended as:
"Both researchers and IRBs should take especial care to ensure that the proposed human subjects *"and / or their legal guardians" (added)* will be able to understand *"the objectives of the research project" (added)* and assess the risks of participation, and that the consent-taking procedure and the documentation are properly designed to achieve this end."

Paragraph 5.70
"In the context of institutions such as hospitals with centralised patient records databases, we recommend that IRBs should take steps to determine who should be the proper administrative custodians responsible for patient medical information in the institution"

This is beyond the scope of IRBs. It should be a policy matter undertaken by MOH/ the institution following legal advice

Paragraph 5.72
"Institutions should ensure that clear formal procedures are laid down for the release of all kinds of patient and medical information, and should formulate these procedures in consultation with their ethics committees."
Problems may also arise with present day computerized records as any one with a password to access the computer may access patient records easily.

Paragraph 6.9
Query whether the requirement that the research proposal must, in the professional judgment of the researcher be ethical in all aspects, is legally binding.

Paragraph 6.11
Who will judge whether researchers are using IRBs and the ethical review process as a means of gaining ethical approval for research projects that the researchers themselves entertain doubts or uncertainties about from the ethical point of view?

Paragraph 6.37
Efforts by researchers to contact and inform the attending physicians, or the institution, consultant or senior person in charge of the department or clinic attending to the research subject of the proposed research programme should be in the form of a **formal** note to the physician to inform them, rather than an informal procedure.

Paragraph 6.39.1
Requirement for researchers to formally contact and inform attending physicians in cases of research involving any level of clinical interaction with patients can become quite touchy as it may result in patient dissatisfaction with previous physicians / surgeons. There may also be some patients who can pose a potential medical legal problem whom the primary provider may not be keen to include in the studies. Professional ethics issues are also involved.
Also, is there a need to obtain permission from the attending physicians?

Paragraph 6.39.2
In the case of research which involves access to patient medical records, but with minimal levels of interaction for the purposes of obtaining more information (for instance, interviewing the subject patient for a history), researchers should *"still be encouraged to" (deleted)* inform the attending physicians, and the IRB *"in its discretion" (deleted)* may make such formal contact and information a condition of ethics approval

General Comment:
It may be pertinent to explore the time frame of storage of project protocols, reviews, materials , etc by IRBs following the completion of the research study, from a medico-legal point of view. Similarly for medical records?

Note: Minor suggestions as to grammatical errors, formatting and spelling have not been included in this summary.

Adding years of healthy life

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7th October 2003

Assoc Prof Terry Kaan
Chairman
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Dear A/Prof Kaan

FEEDBACK ON BAC CONSULTATION PAPER ENTITLED "ADVANCING THE FRAMEWORK OF ETHICS GOVERNANCE FOR HUMAN RESEARCH"

I would first like to commend on the high quality of work done by the BAC Human Genetics Subcommittee. The Consultation Paper issued is indeed comprehensive and "timely" in our cluster's effort to address the potential ethical and legal issues arising from research within the cluster.

In May 2003, an Ad-hoc Committee on Ethics & IRB Review was set up under the advice of CEO NHG to study the report and recommendations made by the MOH Committee of Inquiry arising from the investigation on the NNI's study. The Committee has developed a framework for the implementation of MOH panel recommendations, and recommended critical measures that will strengthen the ethical framework of research in the cluster.

The Committee was also tasked in reviewing the consultation paper, with particular focus on the processes and procedures to be adopted in the ethical governance process and recommendations on the constitution and role of institutional review boards.

In view of the short time frame, the Committee has outlined a few points arising from the consultation paper. These points were viewed as critical and having immediate relevant effects in the cluster's effort to establish a more robust and effective ethics review processes and boards. The Committee will further review the issues outlined in the consultation paper in more details. The views are attached in Annex A.

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On behalf of NHG, I would like to thank your Committee for inviting the cluster to offer our views and comments that will help inform and shape the recommendations, which the BAC will be making to the Government in the form of a proposed Report on the Ethical Governance of Human Research.

Thank you

Yours sincerely

DR WONG JIEUN SHYARD
DEPUTY DIRECTOR
CLINICAL PROGRAM
PROFESSIONAL POLICY & PLANNING

Annex A

FEEDBACK ON BAC CONSULTATION PAPER ENTITLED "ADVANCING THE FRAMEWORK OF ETHICS GOVERNANCE FOR HUMAN RESEARCH"

(A) Recommendation 3 (page 26)
The current requirement that every hospital have an institutional review board should be statutorily formalized, and extended to all institutions that carry out clinical research. Every institution that conducts research, or allows research to be carried out on its premises, or on its patients, or on or involving access to or use of human tissue collections in its custody, or on or involving access to or use of medical records or other personal information in its custody should have an effective institutional review board.

Comments:
With reference to the above recommendation, the Committee felt that this is not fully in accordance with the new ethics review processes and structure that the cluster will adopt, arising from the recommendation put forth by NHG Clinical Research Advisory Committee, chaired by Prof Edison Liu, Executive Director of GIS.

NHG is currently in the process of reconstituting and reorganizing the Institutional Review Board (IRB) into Domain-Specific Review Board (DSRB). DSRB, being non institutional-based, will not satisfy the requirement as stated in the above recommendation that every hospital should have an effective IRB. In the new DSRB system, respective hospitals will not have an IRB. DSRB will be centralized and managed by the cluster HQ. Each DSRB (there are altogether 4) will review and approve protocols for all the institutions within the cluster.

Although item 5.12 describes the possibility of having domain specific IRB, it would probably be better to reformulate recommendation 3 and to include domain specific IRB, which is non institutional-based upfront.

(B) Recommendation 4 (Para 2 and 3, page 29)
The continuing review, supervision and audit (including monitoring feedback from research subjects) of clinical research programmes approved by them. Reporting of the outcomes of the review and audit to proper authorities and to their appointing institutions and to principal investigators of the research programmes.

Reporting on the clinical research programmes and in particular the results of the programme approved by them to the proper authorities and to their appointing institutions, feedback to the constituent researchers of the institutional review board , and monitoring feedback from research subjects.

Comments
With reference to the above recommendation, the Committee felt that a highly trained and efficient administrative support staff would be required to assist the IRB in its recommended role of "continuing review, supervision and audit", particularly since the IRB is only part-time, and the number of protocols to track will multiply over time. The caution really is, would the IRB be able to deliver what is expected. It would be of considerable help if it were mandated that the PI report regularly on the research project.

(C) Item 5.69 Medical Records and Patient Information (page 38)
Medical Records and Patient Information. The BAC recognises that the issues arising from access to the use of and the custody of medical records and other patient information is becoming increasingly complex. In this area, the ethical issues are inextricably interwoven with legal considerations, and the impact of the existing law is currently unclear in many situations. We hope to explore these issues in a separate subsequent report.

Comments
With reference to the above recommendation, the Committee felt that this issue should be explored as soon as possible as the question of whether patient consent is required is being debated in many quarters with differing opinions.

(D) Item 5.73 (page 39)
It is desirable that the IRB should have the ultimate authority and responsibility for the ethical clearance of access to patient medical information within the institution, so that no patient medical information may be released for research purposes without clearance by the IRB. Such authority should by necessity also extend over the administrative custodians of patient medical information.

Comments
The NHG Ad-Hoc Ethics Review Committee had recommended that the custodian of medical records in any institution should be the CMB, Medical Director, or CEO of NHG Polyclinics. In the event that the aforementioned is the PI of a research proposal, the Chairman of the IRB would be the custodian. Thus, the IRB would give the ethical clearance for release of patient medical information, but the final approval would come from the institution's custodian of medical records.

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2nd October 2003

A/Prof Terry Kaan
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Dear A/Prof Kaan

REQUEST FOR FEEDBACK ON BAC CONSULTATION PAPER ENTITLED "ADVANCING THE FRAMEWORK OF ETHICS GOVERANCE FOR HUMAN RESEARCH"

Thank you for your letter of 15 September 2003.

Please find enclosed comments from my main research staff.

Yours sincerely

A/Prof Koh Tian Hai
Medical Director
National Heart Centre

A:bac-021003

MAK Koon Hou

30/09/2003 01:50 PM Dept : Department of Cardiology; National Heart Centre; 17 Third Hospital Avenue; Singapore 168752 Tel : 65-6-436-7545

To: KOH Tian Hai/CARDIO/NHC@NHC
cc: Sally KOK/DIROFF/NHC@NHC, Margaret LIM SH/CARDIO/NHC@NHC

Subject: Bioethics Medical Committee reply

The following are my comments:

1. Training and funding of IRB personnel, especially with regards to monitoring.

2. Multicentre trial should consider having a central IRB comprising of members from each institutional IRB.

3. Patient records for retrospective reviews should be waived. There should be a statement in the hospital attendance for patients to allow their information to be used, in confidentiality, for the purpose of research.

4. Extension of IRB to family and private practitioners

Request for feedback on BAC consultation paper entitled " advancing the framework of Ethics Governance for Human Research"

With Regards to part A:

There is currently a very gray area of what constitutes a drug and non-drug trial.

e.g. for Cardiology, present trials focus on a stents that are drug coated: Is this thus a interventional trial or a drug trial? The consequent EC review of the trial will be different depending on what view the EC takes. The EC should therefore have very clear guidelines on what constitutes a drug and non-drug trial.

There should be open channels of communication between the PI of the protocol and the EC. If need be, direct interviews of the PI by the EC should be conducted to enlightened both the EC and the PI of what are the needs on both sides. In this era of a very competitive spirit of research, this may cut time, because of the quick clarification of issues, for the approval of protocols by EC.

Increasingly, more animal work is being performed. Guidelines for the ethical care of animals should also be addressed in a clear manner. I understand that all issues are addressed with regards to human research only. Will there be separate reviews for animal research?

With Regards IRBs:

It may be pertinent to ensure that IRBs are formally trained and the members of the IRBs made known. This may allow more transparency to the review process. The IRBs bare a heavy burden and if there are many members rotating on the same IRB, a specific quorum should be specified and made public. This may help to enhance the moral authority of the EC.

To further enhance standards, I fully agree with the setting up an overall supervisory authority as stated in Recommendation 7. This will allow the full accreditation of all IRBs. This national supervisory authority may also aid in the same role with animal experimentation issues.

Sincerely,

Philip Wong
National Heart Centre

30 September 2003

Assoc Prof Terry Kaan
Chairman
Human Genetics Subcommittee
Bioethics Advisory Committee
Singapore

Dear A/Prof Kaan,

REQUEST FOR FEEDBACK ON BAC CONSULTATION PAPER ENTITLED "ADVANCING THE FRAMEWORK OF ETHICS GOVERNANCE FOR HUMAN RESEARCH"

Thank you for your letter dated 15 Sep 2003.

The NUH IRB members would like to meet and discuss this consultation but due to the short timeframe, we have not been able to do so.

My initial views, without in-depth consultation and discussion, are as follows :

1) Definition of the Principal Investigator (section 6.23). This should be modified to take into account pharmaceutical company initiated multi-centered, multi-national clinical trials on new drugs. There is often an international committee that designs (and analyses results of) the protocols. The notional PI in Singapore will NOT be involved in many aspects, but will officially be the PI as far as the legal situation goes if your recommendations are implemented. This will seriously deter any local involvement in important multinational clinical trials.

   Within Singapore, that definition proposed is acceptable.

2) Another concern is that there is nothing that addresses Conflict of interest issues. This is quite important in scientific research in a small country like Singapore. Perhaps there should be some mention of this area.

3) Finally, section 5.15.2 mentions that the IRB is supposed to "supervise and audit on a continuing basis" the research programmes. And 5.15.3 mentions that the IRB is supposed to "monitor outcomes" of research and "evaluate" them, provide "feedback and maintain dialogue" with researchers. These 2 points imply that the IRB is also an enforcement agency, with staff to do that sort of work. These tasks will require a totally different mind set from the reviewers who evaluate the ethical and scientific aspects of a study, and are not trained to evaluate how well the implementation is being carried out. The auditing tasks will also require much more resources, than exists at present in Singapore (or in other countries) for IRBs. While I recognise that this is an important area, perhaps a separate audit committee should be responsible

for audit and these other similar tasks, rather than the IRB which approved the protocol.

I have circulated the copies to all the members of the NUH IRB and are awaiting their comments. I shall inform you again, once I have consolidated all their comments.

Thank you.

Yours sincerely

Professor Lee Kok Onn
Chairman, Institutional Review Board
National University Hospital
C/o Medical Affairs Department

cc. Professor Lee Hin Peng
Chairman, IRB
National University of Singapore

Further Comments from National University Hospital IRB

1. Expectation of IRBs to perform the role of "continuing review, supervision and audit" will add considerably to the current workload of IRB members.

2. Adequate resources, such as administrative support, time and training for IRB members would be needed in order to meet the expectations of IRBs.

3. Will IRBs be held responsible for giving approval to a research which later goes wrong?

PARKWAY GROUP HEALTHCARE PTE LTD

29 September 2003

Assoc. Prof Terry Kaan
Chairman
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Dear A/Prof Kaan,

FEEDBACK ON BAC CONSULTATION PAPER ENTITLED "ADVANCING THE FRAMEWORK OF ETHICS GOVERNANCE FOR HUMAN RESEARCH"

Thank you for inviting us to give our views on the above consultation paper.

Our comments relate to the following articles:

1.7 You may wish to add:

- To keep abreast of ethical governance of clinical research in other countries, many of which carry out multicentre studies with centres in Singapore.
  (Rationale: There are some who feel that creating more statutory requirements will discourage research work in Singapore. On the contrary, it will attract multicentre studies and researchers who expect high ethical standards).

2.23 Please note that some changes are imminent, such as the dissolution of the MCRC and the CTCC.

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Recommendations 1 & 2:
One way of implementing these is to expand the purview of the Medicines (Clinical Trials) Regulations 1998 and the SGGCP to include all research studies. Some IRB's are reviewing animal research studies as well.

Recommendation 3:
This may not be necessary, as approval for Clinical Trials is not given unless the trial has been reviewed and approved by an IRB/HEC. It is also not necessary for smaller hospitals which do little research work to form an IRB. They can always ask the IRB of a larger hospital to vet their research work.

5.17 You may wish to add:
If a research study is scientifically flawed, it is unethical to carry it out.

6.5 You may wish to add:
"Researchers and their supervisors are not absolved of responsibility for their work by the existence of the IRB/HEC. The IRB can only give guidance and approval for the application of a Clinical Trial Certificate. Physicians are not relieved from criminal, civil and ethical responsibilities.

The IRB recognizes that the only real protection for the subject lies in the scrupulousness, conscience and personal integrity of the investigator.

7.6 There is a move now for hospitals to adopt the same/similar SOP.

7.10 & 7.11

Accreditation and licensing of Clinical Research Centres and Auditing of IRBs for compliance are now the responsibility of the Health Sciences Authority.

You may wish to touch on the Ethical Training for IRB members and also for Investigators. This is important for successful implementation of your recommendations.

In keeping with Accreditation and Audit of IRB's, there is a need to carry out Ethical Training of IRB members and Investigators. A couple of training programmes are available. One is the FERCAP (Forum for Ethical Review Committees in Asia and the Western Pacific). FERCAP receives support from many institutions such as WHO, CIOMS, UNAIDS, UNESCO and the European Forum for Good Clinical Practice. Another programme is run by the American accreditation body, AAHRPP® (Association for the Accreditation of Human Research Protection Program, Inc®, http://www.aahrpp.org/). Training can be on-line (such as the NIH-OHRP Human Subject Assurance Training) to certify knowledge of "human participation protection".

Recommendation 8:
Most (if not all) Hospitals have Indemnity and Insurance for their IRB members.

In the Private Hospitals and Medical Clinics (Amendment) Act 1999, it is stated that:
"A. Members of the Quality Assurance Committees are protected against legal action when they have acted in good faith.

D. Medical experts appointed by MOH to assist in the administration of the Act, e.g. members of advisory committees, are protected from any personal or professional liability in the exercise of their responsibility and judgement, when it is done in good faith."

Ultimately, it is the sponsor of the Clinical Trial who should provide insurance and indemnity (legal and financial coverage) for the investigator/institution against any claims arising from the trial, except for claims that arise from malpractice and negligence.

Yours Sincerely,

Dr Khoo Chong Yew
Chairman, Parkway Independent Ethics Committee

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30th Sept 2003

Assoc Prof Terry Kaan
Chairman
Human Genetics Subcommittee
Bioethics Advisory Committee

Dear Terry,

RE: REQUEST FOR FEEDBACK ON BAC CONSULTATION PAPER ENTITLED "ADVANCEING THE FRAMEWORK OF ETHICS GOVERNANCE FOR HUMAN RESEARCH"

Thank you for sending me the above paper. First of all let me congratulate you and your Committee for a work well done. It is very comprehensive and complete; the result I am sure of much thought and hard work.

My only comments are a few of not that much import, which I have already discussed with you.

1) In section (v) under "Institutional Conflicts of Interest" para 5.30 "The highest level of governance in an Institution"; is a bit vague for the ordinary reader. You have explained this to me, but I was wondering if it could be modified somehow; especially since the IRB should not report to the Medical Board of the Institution. In fact if I am not wrong, some IRBs do report to the Chairman of the Medical Board.

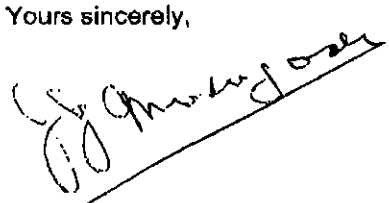
2) The word "Recuse", as you have told me is used in the Legal fracternity but a lay man (doctor) will look it up in the dictionary to find no such verb in the "Queen's English".

3) Under Section (v) "Medical Records & Patient Information" para 5.70 line 5. It may be useful to add the following or such.
"Establish a system through which the custodian only releases the patient medical information (eg the case notes) for the patient follow-up. If they are required for any other purposes such as research, the custodian shall inform the attending physician before releasing ----------.

4) Under Section (vi) "Researchers and Attending Physicians" para 6.37 line 3. "Being attended to by Physicians", ---- it is incumbent on the Researcher to contact and inform the attending Physicians of the proposed research programme.
Para 6.37 line 7 "By different Physicians on their visits," ------ efforts should be made to contact and inform the institution concerned.
(In other words cut out "reasonable" and "on an informal basis")

5) Para 6.39.3
Cut off completely or modify as follows:- In the case of Research which involves access to and study of the patients' medical records without any kind of contact at all between the Researchers and the subject patients, the Researchers should also formally contact and inform the attending Physicians

Yours sincerely,



Dr J J Murugasu BBM
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Senior Consultant
Director of Endocrine Laboratories

8 October 2003

Assoc. Professor Terry Kaan
Chairman
Human Genetics Subcommittee
Bioethics Advisory Committee

Dear Terry

REQUEST FOR FEEDBACK ON BAC CONSULTATION PAPER ENTITLED "ADVANCING THE FRAMEWORK OF ETHICS GOVERNANCE FOR HUMAN RESEARCH".

Thank you for your invitation to submit our views on the Consultation Paper. The Paper is a comprehensive and well-thought out document for which you and your subcommittee deserve every congratulation. SGH IRB has sent its response through SingHealth.

There are two additional comments I would like to make.

1 As the Health Sciences Authority (HSA) is the accreditating authority of the country's IRBs, it should be the HSA which provides the monitors for the institutional IRBs. This does not preclude the individual institution having its own monitors to assist the day-to-day running of the trials. But random checks from an external authority is a great help towards objectivity of the process.

2 Institutions are beginning to realise that research is a communal activity and not the preserve of a few individuals. As such, resources, financial and manpower, must be allocated to ensure the success of the enterprise. An important aspect is the provision for the monitoring of all research. There is a shortage of qualified monitors. This vacuum should be filled at the level of the HSA, to begin with, so that the few now available may be shared. Training scholarships for appropriate candidates, I understand, are already available.

With warm regards,

Swee Eng

Dr Aw Swee Eng
Chairman, SGH IRB

Further Comments from Singapore General Hospital IRB

"It is commendable for the Bioethics Advisory Committee to clarify decisively the broad range of activities that nowadays constitute clinical research and to make the necessary provisions for their ethical governance.

It is also gratifying to note that the paper specifically lays on the researchers the responsibility of making "the first judgement as to whether in their professional judgement, the proposed research is ethical". This will expedite the recognition of the importance of the ethics of research and lead to the growth of ethical education in our young research community.

It is to be hoped that the recommendation... "that institutions have an obligation to ensure that IRBs receive adequate administrative support that is commensurate with their central role in the ethics governance process" will receive a clear, unambiguous response from those in a position to do so.

[Paragraph 5.18] would be cumbersome to realise in practice and could be deleted. It would also be helpful for the IRB always to receive, whenever applicable and available, a summary of the scientific review by the grant-funding agency"

From:
Theresa Chow
Deputy Director, Singapore Tissue Network

Date: October 8, 2003

Dear BAC members,

I would like to thank the BAC for the excellent work in the drafting of the consultation paper which covers all the pertinent grounds in the ethical governance of biomedical research involving human subjects. The recommendations for establishing a unified national framework for the ethical governance and a national statutory agency for the supervision, regulation, accreditation and auditing of the ethics review boards are most outstanding. The effort to place patient's rights as first place is clear, and the recommendations for how to strike a balance for research benefits and protection of patient's rights is elegantly covered. I have only a few comments to make.

Some comments:

"Applicable Principles" (sections 4.4 to 4.17) cover the important rationales behind the underlying principles for ethical governance, that of respect for the individual, respect for free and informed consent, respect for privacy and confidentiality, respect for vulnerable persons and the avoidance of conflicts of interest, or the appearance of conflicts of interest.

In addition to the basic principles, the following sections are of particular interests to me:

Section 4.8: *We recognise, however, that there can be neither absolute certainty or finality as to the precise content of the body of ethical values to be applied in such an assessment. This is so in Singapore, as it is everywhere else in the world. The body of ethics in any given society is neither fixed nor clearly defined for all time, but* ***evolves*** *in response to advances in knowledge, technology, changes in social mores, and community dialogue and debate.*

Section 4.12: *Despite some uncertainty at the edges, a core of universally accepted principles and ethical values lie at the heart of most societies in their application to the protection of human research subjects.*

Section 4.13: *It is desirable that a code of applicable principles for ethical governance be eventually formulated for the* ***common guidance*** *alike of ethics review boards, research institutions, researchers, the human subjects of research and all other parties involved in human research* ***in the interests of consistency and fairness*** *of the judgments of ethics review boards.*

Section 4.16: *We take the view that it is part of the function of a responsive and dynamic system of ethical governance that the applicable body of ethics be reviewed and assessed from time to time* ***to keep it relevant to and reflective of community values and the needs of research.***

Comments:
A national statutory board would be instrumental in defining standards and ensuring that such standards will be adhered to through auditing. In particular, this would provide the proper channel for continuous improvement in policy settings taking into account the changing needs and attitudes of the local community. Guidelines from the national statutory board would alleviate the research communities and ethics committees from uncertainties generated from independent interpretations of recommendations of the BAC, which, without the establishment of a statutory agency, is left up to the individual ethics committee to interpret and implement, creating possible inconsistencies.

- Section 3.6: the BAC's proposed definition of "biomedical research" which should be regulated:

Any research study, trial or activity involving human subjects, human tissue, or medical, personal or genetic information relating to both ***identifiable and anonymous*** *individuals undertaken with a view to generating data about medical, genetic or biological processes, diseases or conditions in human subjects, or of human physiology or about the safety, efficacy, effect or function of any device, drug, diagnostic, surgical or therapeutic procedure (whether invasive, observational or otherwise) in human subjects whether as one of the objectives or the sole objective, of the research study, trial or activity*
and

which the research study, trial or activity has the potential to affect the safety, health, welfare, dignity or privacy of the human subjects involved in the study, or of the donors of human tissue or information used in the research, or of the family members of any of the human subjects or donors thereof, or to which such medical, personal or genetic information relates.

Comments:
This carefully thought out definition has safely bracketed all the categories of research that should be under the purviews of a properly constituted ethics review board including research involving the use of human tissue samples, whether identifiable or anonymized.

The ability to have 'expedited review' for appropriately designed data escrow or other arrangements in which personal and other identity information is securely withheld from the researchers by a third party provider of the information under the above definition undoubtedly will help to expedite research process, particularly in legacy tissues and historical paraffin blocks.

I would like to add that what is worth consideration is the granting of a waiver of consent for research that involves no further direct contact with the patients (examples as in section 5.66), , or if the waiver will not harm the rights and welfare of the subjects, and that if the research cannot be practically completed without the waiver of consent.

Section 3.8 : *We note that there may be some exceptional circumstances in which it may be ethically acceptable to abbreviate or temporarily suspend the usual ethics review procedures and requirements, provided that all the applicable legislative and regulatory requirements are satisfied. We have in mind situations of national security or emergency health situations, in which urgent research may have to be carried out to avert harm to national security or for the urgent protection or*

treatment of whole populations at risk. In such cases, we think that it is permissible for ethical review boards in consultation with the proper authorities to formulate and lay down written guidelines for the exemption or expedited review of defined classes or types of such emergency or urgent research in the national interest.

Comments:
The 'proper authorities' is a vague term and needs clearer definition.

- Ethics Review Boards
  Shared "Domain" and Other Special Ethics Review Boards (sections 5.10 to 5.13)

Comments:
These sections address the need to share ethics review boards when an institution is of a 'small size' or having a 'small number of research proposals' making it impractical to establish and maintain a standing ethics review board of its own.

Alternatively, in section 5.11 , it is stated that it is permissible for several such institutions to jointly appoint a shared ethics review board and in section 5.13 , the mention of a possibility of accreditation given to a commercial ethics review board by the national supervisory agency are all measures which will be essential to support research of a small institution without incurring extra expenses in maintaining a full board for reviewing. Small institutions and private companies conducting research would find this welcoming and necessary.

Section 5.12 -: the mention of a specialist ethics review board or a domain ethics review board having the capacity to assess research in the particular specialist area allows quality review as this would allow special expertise being tapped for the review, and having a core group dealing with a specific research field will allow a continuation of ideas and maximize the lessons learnt as the field evolves with new technologies. This in turn will help to formulate new requirements for review that is in pace with the most current trends and practices.

Responsibilities of Ethics Review Boards

Section 5.15.3 Outcome Assessment, Reporting and Feedback

In this responsibility, ethics review boards (especially those in large institutions with a large number of research programmes) undertake the monitoring and collation of adverse event reports, the outcomes of the research programmes, an evaluation of the actual versus the anticipated outcome or results, and the reporting of outcomes and trends to the relevant authorities and to the institutions that they are appointed by and to whom they are responsible. Another major aspect of this role is the role of ethics review boards in providing feedback and maintaining a dialogue on applicable standards with its constituent researchers. In the discharge of role, ethics review boards can and should also act as the key institutional agency which receives, acts upon and reports to the relevant authorities on concerns and feedback expressed by the human subjects of the research programmes.

Comments:
Clarification is sought from the BAC to define the term 'the relevant authorities'.

Section : Review of Scientific Merits

Ethics review boards are also required to carry out peer or expert assessments of the scientific merits and soundness of proposed research programmes. Thus a proposed research programme may, although it otherwise satisfies all ethical considerations, be properly rejected by an ethics review board on the basis that the scientific objectives of the research programme do not meet the standards set by the institution or the ethics review board. This is a distinct and separate responsibility of ethics review boards. Importantly, the fact that a particular proposed programme of research is judged to be of sufficient scientific merit does not necessarily mean that it satisfies ethical considerations, although in many cases, these two considerations are linked, especially in the assessment of harms versus benefits

Comments:
What will the policies be when differences arise in opinions for scientific merits in the evaluations of the institution, grant funding agency and/or the ethics committee?

The Constitution of Ethics Review Boards

Section 5.22 : *Ethics review boards should not be appointed as ad hoc committees to consider research proposals as and when they arise, although it is acceptable for institutions with standing ethics review boards to appoint special ad hoc committees in consultation with their standing ethics review boards to consider special research proposals. We prefer, in such cases, that the institution works with their standing ethics review board to appoint special subcommittees co-opting experts or reviewers to assist the standing ethics review board in the particular project concerned. For example, an ethics review board may receive a research proposal involving an area of research with which no member of the ethics review board is familiar. In such a case, the institution may work with the ethics review board to identify and co-opt ad hoc experts or reviewers to assist the ethics review board in its assessment and review of the proposal. The co-opted ad hoc experts or reviewers sit as a subcommittee of the ethics review board.*

Comments:
Does the subcommittee has the voting rights or only serves as a review panel?

Composition

Sections 5.26 to 5.27 defines the composition of the ethics review board.

Comments:
To support the concept of an ethics review board being a key full-time management office and not merely as honorary *ad hoc* committee, there is a foreseeable amount of involvement in time and expense. How would the cost of setting up this office be provided for? Would there be a charge levied for the approval? If so, should there be differences in charge structure depending on whether it is an in-house application or from an outside source?

Section 5.27.5 : *Ethics review boards should also have lay, non-scientific or non-medical representation. Where practical, and where the size and volume of the workload of the ethics review board permits, lay representation may include respected lay members of the community, experts in philosophy, ethics, psychology, sociology or the law.*

Comments:
Should the board include a pharmacist and a statistician?

Specific Operating Principles

Section 5.70 : *In the context of institutions such as hospitals with centralised patient records databases, we recommend that ethics review boards should take steps to determine who should be the proper administrative custodians responsible for patient medical information in the institution, and to establish a system through which the custodians would inform the attending physicians before releasing patients' medical information for the purposes of medical research.*

Comments:
This is only possible if approval from the attending physicians is not a necessary condition to be satisfied after informing, provided that the approval for the study and the use of medical information related to the study has been approved by the ethics committee. Otherwise it will slow down the process and would render the process impractical. A clear definition of 'who' are the 'administrative custodians' together with clear procedures for the release of medical information by the designated classes of custodians would be essential, especially in situations where physicians enrolls their own patients for research.

Responsibilities of Researchers

Continuing Responsibilities, Deviation and Variation

Section 6.28 *A research project may also expand in scope, in its objectives, or in the researchers involved – some researchers may resign, or decide to take a less active role, while other researchers are recruited. Or it may be discovered that a proposed course of action poses greater risks than originally assessed for the proposed subject population, or that the trial has resulted in greater harm (whether of degree or of incidence) then originally contemplated. Or it may be discovered in the course of the trial that some part of the original protocol as proposed in the ethics review application has not been strictly adhered to, although such departure may have been made in good faith by mistake or by necessity, out of consideration for the welfare of the subjects.*

As part of their continuing responsibilities stated in paragraph 6.29 above, the Principal Investigator(s) in particular is under a strict obligation to immediately and in writing seek approval for any changes where such changes have no yet been made, or otherwise report any changes where such changes have already been made, to the ethics review board by which initial research application was considered and approved. The Principal Investigator(s) shall in their request or report detail the

changes, giving their objective assessment of any impact and consequences (both from the clinical and ethical points of view) of the changes.

Comments:
The statement "or otherwise report any changes where such changes have already been made" alludes to the fact that un-approved changes are allowed. Can the BAC elaborate under what unusual circumstances (besides that stated in section 6.33) that changes are allowed without first informing the ethics review committee to obtain approval before implementing the changes?

Section 6.33 *Minor changes intended solely for the greater safety, health, welfare and well-being of the human subjects taken after consultation with all researchers involved in the trial need not be immediately reported to the ethics review board. For example, if it appears to a researcher that a particular research subject is not altogether comfortable with one of the planned procedures, that procedure may be dropped and the research programme varied to such extent, without the need for immediate reporting. Reporting of such changes by the Principal Investigator to the relevant ethics review board should however take place as soon as may be practicable. But other changes, minor or otherwise, made for the greater effectiveness of the trial or of its objectives do not fall within this category and should be immediately reported.*

Comments:
Can the BAC consider the option of expedited review for minor changes made for the greater effectiveness of the trial provided that the change does not increase risks to the patient's health or welfare?
Researchers and attending physicians

Section 6.35 *Where a proposed researcher is the attending physician, the researcher / physician should be aware of a potential conflict of interest, and of the fact that their patients may feel obliged to give consent. We repeat and endorse Article 23 of the Declaration of Helsinki, which states that "[w]hen obtaining informed consent for the research project the physician should be particularly cautious if the subject is in a dependent relationship with the physician or may consent under duress. In that case the informed consent should be obtained by a well-informed physician who is not engaged in the investigation and who is completely independent of this relationship".*

Comments:
Can one further define the "researcher / physician"? Currently, a lot of research projects involve collaboration between an attending physician and a researcher at an institute. The administration of informed consent is often conducted under that setting. Is a physician who is named as a co-investigator in a project, who enrolls patients from his patient pool, supplies medical information with informed consent, but does not handle the samples for research a researcher / physician?

If he/she is defined as such, then the engagement of another informed physician could be a potential issue, as almost all physicians are busy, and it would take a lot of convincing to engage another physician.

Does the consenting need to be done by another independent physician or can it be done by a consenting nurse as physicians have a very busy schedule?

If a nurse is administering the consent, can the nurse be someone working for the researcher/physician? According to section 6.17, where it is stated that: "*we exclude from the definition of researcher persons acting only in an administrative or support capacity, and who are under the direct supervision and control of a researcher. Examples of such research support personnel would be administrative clerks and nurses assisting in clinical duties."* **Does this exclusion apply to the nurse working for a researcher/physician who sees patients in a physician/patient setting?**

For the statement : *"[w]hen obtaining informed consent for the research project the physician should be particularly cautious if the subject is in a dependent relationship with the physician or may consent under duress.* **Would a standard statement in the consent form to the effect that the patients are free to decide whether to participate, and that their decision will NOT be affecting their medical treatment in anyways sufficient to address this possible conflict of interest?**

Section 6.37 *We further take the view that where researchers are aware that the proposed research subjects are currently receiving treatment or otherwise being attended to by physicians, reasonable efforts should be made on an informal basis by the researchers to contact and inform the attending physicians of the proposed research programme. If the research subjects customarily attend at a hospital or clinic, and are attended to by different physicians on their visits, reasonable efforts should be made on an informal basis to contact and inform the institution concerned, and the consultant or senior person having* charge *of the department or clinic concerned.*

Section 6.39.2 *In the case of research which involves access to patient medical records, but with minimal levels of interaction for the purposes of obtaining more information (for instance, interviewing the subject patient for a history), researchers should still be encouraged to contact and inform the attending physicians, and the ethics review board may in its discretion make such formal contact and information a condition of ethics approval.*

Section 6.39.3 *In the case of research which involves access to and a study of patient medical records without any kind of contact at all between the researchers and the subject patients, the ethics review board need not require researchers to formally contact or inform the attending physicians (on the assumption, of course, that they have complied with all other applicable requirements).*

Section 6.39.4 *We take the view that efforts to contact and inform the attending physician(s), or the consultant or senior person in charge of the department or clinic concerned, should be made before commencement of the research project. Where this is not possible, such contact must be made as immediately after commencement of the research project as may be practicable, as the ethics review board may direct.*

Section 5.70 *"In the context of institutions such as hospitals with centralised patient records databases, we recommend that ethics review boards should take steps to determine who should be the proper administrative custodians responsible for patient medical information in the institution, and to establish a system through which the custodians would inform the attending physicians before releasing patients' medical information for the purposes of medical research."*

Comments:

Given the complexity of how medical information should be handled, it is best that there be clear policies and standard operating procedures to be set out for

the access of medical information. We hope that there would be guidance as to when to 'inform' versus 'inform and obtain approval' with regards to release of medical information and under what circumstances these modes of action should apply. It would be helpful to list the different scenarios of who would be asking for access to medical information and issuing guidelines for the proper procedures to follow.

Section 8: The protection of ethics review boards

Comments:
An excellent recommendation. This is what is needed most for the establishment of vital ethics committees that can attract a consistent pool of members, ethics assurance auditors, ethics investigators or members of committees of inquiry.

EMAIL RESPONSES TO THE CONSULTATION PAPER "ADVANCING THE FRAMEWORK OF ETHICS GOVERNANCE FOR HUMAN RESEARCH"

Professor Miranda Yap, Director, Bioprocessing Technology Centre

"I endorse what is being proposed in the Ethics Governance Consultation Paper for human research ... The recommendations such as setting up Institutional Review Boards, developing a national and unified framework for processes and procedures, highlighting roles and responsibilities of researchers doing clinical research in Singapore covered by the paper appear to be comprehensive and implementable."

Professor Edison Liu, Executive Director, Genome Institute of Singapore

"[With reference to paragraph 5.16.1 – Review of scientific merits.] The BAC subcommittee should consider the following possibility – that the IRB may accept the recommendations of, or delegate the primary scientific review to an officially constituted scientific review board. Such a board, progressively common in active research institutions, provide the scientific coordination and review in progressively complex experimentation. The ethics review board, then will expedite its scientific review and concentrate on the procedural, ethical and social implications of the research.

[With reference to paragraphs 6.38, 6.39 and 6.19.1] This is ambiguous and confusing...This may lead to a completely impracticable situation when there are many attending physicians that rotate (as in medical schools), or that, more commonly now than ever, there are several key doctors for the patient... In addition, is it required that the researcher have written acknowledgement from the attending physician, or the attending physician refuses to acknowledge the research. Can the attending physician bar the patient from participating even if the patient wishes to join a study?... I believe that this section is not enforceable unless as a recommendation of proper etiquette or as guidelines of behaviour and not as requirements."

A/Prof Chong Siow Ann, Director of Research and Member of Clinical Research and Ethics Committee, Institute of Mental Health

"In most institutions, the medical board is considered the senior management, and it may not be desirable to give the impression as that the IRB could report to a single person like the CEO.

I'm not particularly clear about the examples in which an exemption can be made from review or an expedited review may be permitted, does it include case reports? An example given is the analysis of patient information without any interaction with the patients themselves – this could be interpreted to include retrospective case reviews in which patients' medical records are accessed, but...the Committee has stated the complexity of this issue and has yet come to any conclusion.

It is recommended that a well-informed physician who is not involved [in the proposed research] should take the consent. I'm not certain of how this could be achieved practically – would [this] be left to the judgement of the physician/researcher? In which case, if the physician has indeed deemed that no such factors were present at the times of obtaining the consent, but subsequently an allegation is made that the consent was taken under some duress, how could this then be resolved? On the other hand, the recommendation that consent should be taken by other physician not involved in the study might not be very practical given the amount of clinical work that most physicians have to do.

I agree with all 8 recommendations."

Dr Ang Ah Ling, Chairman, Clinical Research and Ethics Committee, Institute of Mental Health

"I agree with the views expressed by the [Human Genetic Subcommittee] (HGS) and their recommendations. However I would expect that in the eventual implementation of these recommendations, there may have to be changes made as long as the underlying guiding principles are adhered to. For example, the [National Healthcare Group (NHG)] Clinical Research Advisory Committee has recommended the restructuring of IRBs into Domain-Specific Review Boards (DSRBs) and this is likely to be adopted by the NHG cluster. Hence the HGS's recommendations for IRBs will have to be adapted for application to the DSRBs."

Mrs Tay-Png Hong Lan, Deputy Director (Administration), Institute of Molecular and Cell Biology

She suggested that "research trial" be used in place of the term "clinical trial" and that human research should include research using "human tissue material". She also proposed to specify for the length of time for ethics review. She further recommended that the IRB include biomedical scientists or invite them to form an ad hoc panel or subcommittee. The term of the IRB members and their roles and expertise should be stated clearly.

Dr Chay Oh Moh, Chairman, IRB, KK Women's and Children's Hospital

"In general, I don't see [any] major conflict with our [standard operating procedures].

The idea of a national framework for ethical governance and to streamline clinical research involving human subjects is good for transparency and is beneficial to study subjects. Accreditation of IRB is what we are also working towards. Having protected time for IRB members will be ideal.

However, the definition of research on human subjects was taken to also include review of medical records. This will have impact on many small projects such as retrospective studies, audit of clinical practice. This will increase the job scope of IRB by a large proportion as most institutions will have many such studies ongoing often

times. They may not be so time-consuming but nevertheless will add [on to] our already busy schedule.

Recommendation 8 is important for IRB to discharge effectively their duties and I strongly support this."

National Medical Ethics Committee

Name	Feedback
Ms Ang Beng Choo	Very comprehensive paper. Paras 6.37 and 6.38 cast some uncertainty on the existence of attending physicians. It is the responsibility of the researcher to confirm this information with the proposed research subjects. The researcher should emphasise to the proposed research subjects that it is in their interest to declare if they are receiving treatment or under the care of a physician.
Dr Lee Kheng Hock	Comprehensive and well argued paper. To convey his compliments to Prof Terry Kaan and committee for their fine effort.
A/Prof Lee Kok Onn	Initial views (due to time constraints) without in-depth consultation and discussion with other NUH IRB members are as follows: 1. Definition of the Principal Investigator (section 6.23). This should be modified to take into account pharmaceutical company initiated multi-centered, multi-national clinical trials on new drugs. There is often an international committee that designs (and analyses results of) the protocols. The national PI in Singapore will NOT be involved in many aspects, but will officially be the PI as far as the legal situation goes if your recommendations are implemented. This will seriously deter any local involvement in important multinational clinical trials. 2. Within Singapore, that definition proposed is acceptable. 3. Another concern is that there is nothing that addresses Conflict of interest issues. This is quite important in scientific research in a small country like Singapore. Perhaps there should be some mention of this area.

Name	Feedback
	4. Section 5.15.2 mentions that the IRB is supposed to 'supervise and audit on a continuing basis' the research programmes. And 5.15.3 mentions that the IRB is supposed to 'monitor outcomes' of research and 'evaluate' them, provide 'feedback and maintain dialogue' with researchers. These 2 points imply that the IRB is also an enforcement agency, with staff to do that sort of work. These tasks will require a totally different mind set from the reviewers who evaluate the ethical and scientific aspects of a study and are not trained to evaluate how well the implementation is being carried out. The auditing tasks will also require much more resources, than exists at present in Singapore (or in other countries) for IRBs. While I recognise that this is an important area, perhaps a separate audit committee should be responsible for audit and these other similar tasks, rather than the IRB which approved the protocol
Dr Lim Sok Bee	I have discussed with Prof K O Lee and I am in support of his views
Prof Ong Yong Yau	The paper is all encompassing and well thought out. May have some practical problems for implementation e.g. full time ethics Committee.
Dr A Vathsala	1. I agree fully with the current document to include all research proposals including retrospective analyses of outcomes of accepted therapeutic maneouvers to EC for approval. Nevertheless, I write to point out that the vast number of studies and publications from Singapore actually fall into this category. Thus at the practical level, incorporating such a schema in Singapore immediately may nevertheless create the following problems: a. Overwhelm existing IRBs/ECs thereby preventing efficient processing b. Stifle applications especially by junior investigators c. Limit serendipitous discoveries that may yet have clinical importance and potentially benefit patients Given that the current document actually proposes expedited approval of such forms of research by the Chairperson of the EC, it may be worthwhile considering a different and simplified SOP for all retrospective analyses where there is no interaction

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	between the investigators and patients (including investigations or therapeutic interventions). In fact, for the most part such analyses may require access to medical records of patients and consent from the Departmental Head /Attending Physician. A simplified SOP without recourse to an IRB/EC should be considered so as to avoid unnecessary delays in processing these research proposals. 2. I particularly support the need for establishment of national standards for ECs and IRBs. In particular, I write to offer 2 suggestions that may further enhance the ethical review of research proposals. a. Firstly, there may be a need for ECs to have access to an expert panel for various conditions. This may be necessary especially if the expertise within a particular institution or organization on that aspect of health care is limited. The CTCC may be particularly vulnerable to such a dilemma. While I note that the Current document proposes that the IRB/EC has the option to discuss issues of Concern with the researcher himself, the IRB/EC should have the option to call in for expert opinions either from Singapore or outside, especially from those experts in the field who are not involved in the research proposal. Ministry and the national supervisory body should have a panel of experts that they can easily access for such situations. b. Furthermore, a national level EC/IRB may be necessary at times to directly address either appeals from individual researchers or to assist ECs in resolving very difficult ethical research issues. 3. The greatest difficulty I see in the proposal is the lack of enough Clinicians/Scientists in Singapore with the caliber and experience needed to carry out the mandate of this document. As such, it may be necessary for many hospitals to share IRBs/ECs so as to capitalize on this limited expertise.

Professor Goh Chee Leok, Chairman, Research Ethics Committee, National Skin Centre

"This paper is very comprehensive. I have no comment except in item 6.10 where I think it is not necessary for the PI to submit different protocol from their funding application so long as there [is] adequate information and [is] presented in [the] format required by the IRB. PI may be encouraged to provide [an] addendum to provide more details in the study methodology if so needed."