

**SUMMARY OF SUBMISSIONS AND RESPONSES**  
**CODE OF PRACTICE FOR THE EXPOSURE OF HUMAN SUBJECTS TO IONIZING RADIATION FOR MEDICAL RESEARCH PURPOSES**

SUBMITTER	COMMENT	RESPONSE
<p><b>01</b> Richard Smart PHD Principal Physicist &amp; RSO St George Hospital, NSW</p>	<p>A little typo in the <b>RIS</b> has been brought to my attention. The table on page 17, 2nd line down refers to Clause 1.3 instead of 1.4. One of my colleagues was trying to find the reference to clinical trials and missed it in the Scope (1.4) because of this typo.</p> <p>One useful thing that did come out of the discussion at HURSOG which the WG may need to consider is a reference to the Trial Sponsor for projects involving multi-centre clinical trials. For example, if 6 Sydney hospitals are all involved in the same trial, the Regulatory Authority does not want to receive 6 separate requests for approval. Ideally the Sponsor should coordinate the requests from each hospital so that a single submission is made. While I cannot see how we could make this a mandatory requirement it would be useful if the Code gave a recommendation along those lines. This issue has cropped up recently here in Sydney so is a real issue.</p>	<p>Noted. RIS is to be reviewed in light of changes to the Code</p> <p>The role of the regulatory authority in checking dose estimates and risk assessments has been assigned to medical physicists</p>
<p><b>002</b> Sarah Wong Radiation Protection Div EPA, SA</p>	<p>RE: Projects involving multi-centre clinical trials I can understand the issue if the Regulatory Authority has to assess 6 separate requests for approval. Fortunately to date, SA has not received such requests from various centres, maybe I have said too soon!</p>	<p>The role of the regulatory authority in checking dose estimates and risk assessments has been assigned to medical physicists</p>
<p><b>003</b> A/Prof Christopher Rowe Austin Hospital</p>	<p>I am very active in this area as Director of the Department of Nuclear Medicine and Centre for PET, Austin Hospital and most of my studies involve exposure of 4-8 mSv. The higher figure is when comparison of a new tracer to FDG PET is required. My research is primarily in dementia and therefore requires elderly, age matched normal controls. There is no information about the risks in the elderly which I believe are considerably less. Is this correct? Are there accepted risk estimates by age? If so, it would be very helpful to have the figures and it may be appropriate to include them in the Code of Practice.</p> <p>Otherwise I found the draft to be quite good and see no problems with it.</p>	<p>There are risk estimates available in the EC document referenced. Annex 1 will be amended to include this information.</p>
<p><b>004</b> Dr G Dobb Chairman Mount Hospital Ethics Committee</p>	<p>Please be advised the Mount Hospital Ethics Committee have had few applications that have involved the exposure of human subjects to ionizing radiation for medical research purposes.</p> <p>Applications that have had involved exposure to ionizing radiation have been</p>	<p>Noted</p> <p>Noted. Clause 2.1.6 requires independent verification of the</p>

	<p>sent for review by an independent person with expertise in this area.</p> <p>This advice has assisted the Committee and we would support any code of Practice including such provision.</p>	assessment
<p><b>005</b> Dr Adrian Groessler Executive Director of Medical Services Chair Human Research Ethics Committee Rockhampton Health Service District</p>	<p>Our Committee members reviewed the draft copy of the “Code of Practice” having no submissions to put forward. We however would very much appreciate the final copy of the publication of the “Code of Practice” and “Regulatory Impact Statement”.</p>	Noted
<p><b>006</b> Professor Hugh Dickson Chairperson Research Ethics Committee South Western Sydney Area Health Service</p>	<p>The SWSAHS HREC consider this to be a very sensible approach and wish to endorse Option 3 ‘Implement a revised national code of practice.’</p>	Noted
<p><b>007</b> Johathon Thwaites RSO, University of WA</p>	<p>I have reviewed the draft code and have a few comments to make. I have spent the past 23 years working in radiation safety and have completed many assessment for Human Subjects research, inadvertant exposure of pregnant mothers or otherwise in medicine. I also have spent many years carrying out QA on medical x-ray machines.</p> <p>My comments</p> <p>From experience the projects often lacked a closure statement. There needs to be a requirement for closure of a project. This should be in the form of a brief report to indicate the date exposures or the project ceased, a summary of the number of exposures, number of subjects actually exposed, the actual doses given, age and other relevant information of the subjects.</p> <p>If a project is abandoned after a number of exposures have been given because of lack of grant funding, incompetence of organisers or whatever, why this happened.</p> <p>The closure document should also contain a statement as to whether the project had a net positive benefit (ie the Justification issue was address</p>	<p>This requirement is covered in clause 2.38 of the National Statement on Ethical Conduct in Research Involving Humans</p>

	<p>adequately) and briefly what it was.</p> <p>This closure statement should be a requirement of the Committee and the Researcher and so would be an extra point at 2.1.14 and 2.3.4.</p>	<p>Acknowledged, however this is not specific to the use of radiation in research.</p>
<p><b>008</b> Jill Hambling Secretary, HREC-A and HREC-D, St Vincent's Hospital</p>	<p>The following comments on the drafts are made on behalf of the Human Research Ethics Committees (HRECs) at St. Vincent's Health.</p> <p><b>Code - Section 2.2 <i>Subjects or Guardians of Subject</i></b></p> <p>This entire section covers matters that are the responsibility of the researcher. 2.2.1 is a responsibility of the researcher and is covered at 2.1.4. 2.2.2 is a responsibility of the researcher and is covered at 2.1.5. 2.2.3 is a responsibility of the researcher and is covered at 2.1.13. This also seems an unlikely possibility. Who amongst us has a written record or accurate recall of our radiation exposure, let alone the dose received? 2.2.4 is covered at 2.1.6. Withdrawal from a research study is a right, not a responsibility. It is the researcher's responsibility to make sure the research participant is aware of this right.</p> <p><b>Code - Section 2.3.2(a) <i>Human Research Ethics Committee</i></b></p> <p>AND</p> <p><b>RIS - Clause 49 <i>Information Asymmetry</i></b></p> <p>It would be very useful if sample ionizing radiation exposure risk statements for use in the participant information and consent form were included in the Code. Plain English, easy to understand statements are preferred. At present, such statements are often laborious and hard to fathom, which is contrary to the principles of informed consent. Ionizing radiation warnings that are hard to read or unnecessarily lengthy distract the participant from other more serious risks associated with the research intervention.</p> <p>Sample statements would encourage uniformity in Australian research.</p> <p><b>RIS - Clause 64 <i>Self regulation by the Industry – Benefits</i></b></p> <p>Over the years there has been a tendency for various groups to transfer responsibilities to, or add to the workload of, HRECs and their institutions. This has always been without any transfer of resources to support either implementation of the transfer or the ongoing associated responsibilities.</p>	<p>Clause 2.2 removed. Relevant issues covered in clause 2.1 or NHMRC National Statement</p> <p>Researchers are required to provide basic dose on the patient information statement.</p> <p>Accepted. Sample risk statements will be included in advisory material in Annexes</p> <p>Noted</p>

	<p>HRECs are not able to absorb any further workload without the provision of the required resources, including expertise.</p> <p>The HRECs commend your efforts in maintaining a national focus and supporting a national approach to research-related matters.</p> <p>Thank you for the opportunity to comment on the draft documents and for considering this submission.</p>	
<p><b>009</b> Morri Facci Vic Department of Human Services</p>	<p>In terms of the three options outlined in the RIS statement, it is the view of the Radiation Safety Program (RSP) that option 3 is the only feasible option. A replacement of the ARPANSA <i>Code of Practice for exposure of Human Subjects to Ionizing Radiation for Medical Research Purposes 1984</i> is long overdue. To do nothing is not, in the opinion of RSP, an option, as it does not serve to ensure that a uniform approach is achieved both at a national level and at a local level amongst researchers.</p> <p>Based on the deficiencies of the current <i>Code of Practice for exposure of Human Subjects to Ionizing Radiation for Medical Research Purposes 1984</i> it is the preference of the RSP that the revised Code of Practice should also include a Safety Guide. The use of a Safety Guide would eliminate legally problematic ‘should’ and ‘must’ clauses from the Code and also provide a useful tool to elaborate on such issues as risk statements, justification of research and the definition of volunteers and medical benefit. This would help to clarify current misunderstandings of researchers. This information is presently lacking from the current Code of Practice.</p> <p>Other specific comments regarding the draft Code of Practice are summarised as follows:</p> <p><b>Clause 1.4</b> The scope describes where this COP applies but fails to use the term volunteer. It has been commonplace to refer to persons participating in research as ‘volunteers’ and hence this term should be used. Furthermore the Code of Practice should include a definition of a ‘human subject volunteering for research’. The Victorian Radiation Advisory Committee has recently reviewed this issue and have found it more appropriate to define one by exclusion.</p> <p><b>Clause 1.4 lines 15-17 &amp; 19-21</b></p>	<p>Agreed. Advisory material included in Annex</p> <p>Risk statements have been added to Annexes. Justification of research is the domain of ethics committees</p> <p>The scope now includes healthy volunteers</p> <p>Not the role of the Code rather researchers should refer to the NHMRC National Statement on Ethical Conduct in Research Involving Humans.</p>

	<p>In the PURPOSE it refers to ‘human subjects’ whereas in the SCOPE it refers to ‘human research subjects’. In addition, the document then only refers to these volunteers as ‘subjects’. The terminology needs to consistent throughout the document. As previously mentioned, this term should also be defined.</p> <p><b>Clause 1.4 lines 19-23</b> The document really needs to define ‘a medical benefit’. From experience the term medical benefit has been open to interpretation. Researchers have commonly quoted that ‘knowing the results from a DEXA scan or a chest radiograph being reported on’ is a medical benefit. From a radiation protection point of view this is not the case and hence the term ‘medical benefit’ needs to be put into context from a research purpose. For example, any radiation exposure resulting from the research needs to be justified on the basis that this research will provide a benefit to society. A commentary of what constitutes ‘medical benefit’ should ideally be located in the safety guide.</p> <p><b>Clause 1.4 lines 30-32</b> The COP should not exclude pharmaceuticals or medical devices approved by the TGA? Research involving human volunteers is routinely conducted using TGA approved devices and pharmaceuticals. Hence this statement seems to be not warranted.</p> <p><b>Clause 2.1.1(a): lines 68 – 70</b> This requirement is redundant based on the requirement of 2.1.1(c). In order for somebody to comply with the regulatory requirements they must have already considered them. In addition, from a regulatory perspective it would be impossible to evaluate and enforce this requirement.</p> <p><b>Clause 2.1.2(b) lines 79 &amp; 80</b> Preferred text: ‘ <i>the justification for exposing human subjects to ionizing radiation for the purpose of the research;</i>’</p> <p><b>Clause 2.1.2(b) lines 82-85</b> The sub-clause should also require the estimation of the maximum absorbed dose to the skin averaged over any 1 cm<sup>2</sup>, where relevant (this item is referenced further in the document in Section 2.1.7(d))</p>	<p>Using ‘human participants’ in accordance with NHMRC National Statement</p> <p>The use of additional radiation is considered more important. Reference to ‘medical benefit’ removed and the definition focussed on additional radiation.</p> <p>Accepted. Reference deleted</p> <p>Accepted</p> <p>Not accepted. Existing wording encourages justification of the use of radiation over other means rather than just amount of radiation</p> <p>Not accepted. The Code should be broad with respect to this.</p>
--	--	--

	<p><b>Clause 2.1.3 (a)(iii) lines 116 &amp; 117</b> At this point in the document the term ‘health or medical authority’ is used (and is the only place it is used). For consistency, the term ‘relevant regulatory authority’ should be used, as this is the term used throughout the document.</p> <p><b>Clause 2.1.3 (a)(iii) line 117</b> The document states ‘with the permission of the parents’ should be replaced with the term ‘with the permission of the legal guardian’.</p> <p><b>Clause 2.1.3 (b)(i) line 122</b> The word ‘problems’ should be replaced with the word ‘conditions’.</p> <p><b>Clause 2.1.3 (b)(ii) line 126</b> It only became apparent from further reading of the document what was meant by ‘and the risks are minimal’. This statement should quote/reference Annex 1.</p> <p><b>Clause 2.1.4: lines 136-139</b> This statement indicates that the researcher must provide the subject with sufficient information about the ‘associated risks’. The Radiation Safety Program currently has standardised risk statements, which were developed in consultation with an ethicist. It is the preference of the Radiation Safety Program that this document should promote the use of standardised risk statements. As previously advised by the ethicist, any risk statements should have some comparative risk values in them in order for the volunteer to gain some feeling as to the magnitude of the risk. These ‘associated risks’ should be in a form that is easily understood by the volunteer and compares the risk to risks associated with every day events. (For example see IRPA Proceedings P-10-149 Research Protocols using Ionising Radiation in Human Volunteers - Communicating the Risk to the Volunteers (<i>R.C. Smart, J.E. Towson, B. Walker and L. Collins</i>))</p> <p><b>Clause 2.1.5 line 141</b> ‘including the case of irradiation of a child’ is redundant. Children are never in a position to give informed consent and hence this is covered by the preceding statement (line 140).</p> <p><b>Clause 2.1.7(b) lines 154-155</b></p>	<p>Clause removed</p> <p>Clause removed</p> <p>Accepted</p> <p>Accepted and clause amended</p> <p>Risk statements to be included in annexes</p> <p>Not accepted</p>
--	---	---

	<p>Typically it is not the responsibility of the researcher to keep the radiation dose to the human subjects to the minimum level, it is the responsibility of the operator of the equipment or the physician prescribing the radiation dose to ensure this. In most instances the researchers request an ionizing radiation procedure to be conducted and this is performed by radiology, nuclear medicine or radiotherapy personnel.</p> <p><b>Clause 2.1.8 lines 160-161</b> From a regulatory perspective it is impossible to evaluate and enforce if a researcher has ‘assessed’ whether the cumulative dose has exceeded the dose constraints. The researcher should be able to provide a clear statement as to why the dose constraints cannot be met and the implications for the project should be required.</p> <p><b>Clause 2.1.9 lines 162-165</b> This seems to be placing much more onus on the Regulator than is currently the case in Victoria, at least, since normally research protocols are only submitted for regulatory review after they have received approval of the HREC. It is the role of the HREC to assess and approve/justify research where dose constraints are exceeded. The HREC should really be required to provide a justification for exceeding the dose constraints to the regulator and not the other way around, ie. Receiving advice from the regulator.</p> <p><b>Clause 2.1.10 lines 166-168</b> It is suggested that this text should be replaced with the following: <i>The research must ensure that the records of human subjects included consent forms; radiation dose records and details of the research undertaken are maintained.</i></p> <p><b>Clause 2.1.11 line 169</b> The word ‘research’ should be inserted before proposal.</p> <p><b>Clause 2.2.1: line 193</b> The word ‘objects’ be replaced with ‘objectives’ for clarity.</p> <p><b>Clause 2.2.1: line 196-197</b> For regulatory convenience this should be a separate sub-clause as this statement includes two ‘musts’.</p>	<p>Acknowledge with additional advice regarding optimisation in the annexes</p> <p>Clause has been changed so that emphasis is on assessment by radiation medical physicist and requirement for researcher to obtain such an assessment.</p> <p>Clause has been changed to ensure advice is obtained from medical physicist.</p> <p>Clause removed. Retention of records is required for all research. Only record management of novel use of radiation now specified in clause 2.1.7 (f)</p> <p>Clause removed and now covered by clause 2.1 or National Statement</p> <p>Clause removed</p> <p>Clause removed</p>
--	---	---

	<p><b>Clause 2.2.2: line 199</b>  ‘including the case of irradiation of a child’ should be removed as children are never in a position to give informed consent and hence this is covered by the preceding statement (line 198).</p> <p><b>Clause 2.2.4 line 206-207</b>  This is not really a responsibility of the human subject or guardian. This is a ‘right’ of a human subject or guardian and hence should not be included under the heading of the ‘Responsibilities of the Subjects or Guardians of Subjects’. This issue has been adequately covered in Section 2.1.6. It may even be considered that this statement is exceeding the scope of this Code, as this is a general requirement of any research.</p> <p><b>Clause 2.3.2(c) &amp; (d): lines 221 – 227</b>  (Also see comment 2.1.9) Once again this seems to be placing much more onus on the Regulator than is currently the case in Victoria, at least, since normally research protocols are only submitted for regulatory review after they have received approval of the HREC.</p> <p><b>Clause 2.3.2(f): line 230</b>  Insert the word ‘radiation’ before the word ‘doses’.</p> <p><b>Clause 2.3.3: line 232-239</b>  The sub-clause (lines 236-239) ‘Human Research Ethics Committees must therefore ensure that they have access to appropriate radiation advice sufficient to permit a full understanding of the radiation aspects of the proposed research prior to recommending that such research proceeds.’ seems to be the main part of the clause. Lines 232 to 236, that is, ‘A recommendation from, or an approval issued by, a Human Research Ethics Committee indicating that the proposed research meets ethical requirements carries the implication that the Human Research Ethics Committee has considered the radiation related risks of the proposed research.’ is mere commentary that would be more appropriate to appear in a Safety Guide and not in the Code. At a minimum, the clause should be turned around and lines 236-239 should precede lines 232 to 236.</p> <p><b>Clause 2.4; Lines 241 to 244</b>  Some responsibility with the overall observance of this Code should lie with either the principle researcher and/or the Organization conducting the</p>	<p>Clause removed</p> <p>Clause removed</p> <p>Regulatory authority is now referred to as a possible source of further advice</p> <p>Clause removed as it is covered in NHMRC National Statement and is not specific to radiation</p> <p>Clause has been removed</p> <p>An additional clause has been added for the HREC to check that advice regarding dose estimates and risk assessment has been independently verified and provided by the medical radiation physicist</p> <p>The role of responsible person has been removed from the Code as the Code does not deal with responsibilities for</p>
--	--	---

	<p>research. The definition of the responsible person does not capture either the principle researcher and/or the Organization. Using the definition in the Code either the Company/Radiation Safety Officer owning and/or having control of the equipment is responsible and not the research company/person instituting the research. The research company/person can sometimes be a third party entity to the place where the exposure to ionizing radiation takes place. It would make sense to capture research company/person in addition to the facility at which the exposure to ionizing radiation is taking place as being responsible for the overall observance of this Code.</p> <p><b>Clause 3. Lines 254 – 262</b>  This statement is a little bit ambiguous and tends to imply that approval from the regulatory authority is required prior to the HREC giving approval. Vis-à-Vis 2.1.9 lines 162-165, and, 2.3.2 (d) lines 224 – 227.</p> <p>Also refer to 2.3.3 in which it states that the HREC has assessed and considered the radiation related risks of the research. The implication is that this done prior to it being submitted to the relevant regulatory authority.</p>	<p>radiation sources. Responsibilities are limited to ensuring accurate radiation related information is provided to HREC and research participants and that general radiation protection requirements are met in administration of ionizing radiation.</p> <p>Advisory material regarding sponsored multicentred trials has been included in Annex 3  Agree. Responsible person is appropriate where responsibility for sources of radiation(equipment) is focus of the control</p> <p>This requirement has been replaced with a requirement for independent verification and suggestion that further information be sought from the regulatory authority</p> <p>This process has been modified and now requires independent verification by a radiation medical physicist</p>
<p><b>010</b>  Kevin C Allman  Director, Nuclear  Cardiology Services  Concord Hospital/  University of Sydney</p>	<p>The draft guidelines for use of ionising radiation in medical research are unacceptable to responsible medical researchers.</p> <p>The considerations raised are based on theoretical estimates of possible effects based on data which have not been obtained from subjects who have received radiation in research studies.</p> <p>The limits proposed are overly onerous and essentially dismissive of the potential importance of the findings from medical research studies for the future good of the community.</p> <p>I am unclear as to which of the co authors of the draft represents the interests of medical researchers?</p> <p>A review of many recent studies for example, in the fields of interventional cardiology or cardiac PET research will show that a number of important studies demonstrating efficacy of novel interventions or therapies which involve serial imaging of patients or else imaging of patients with several complementary modalities could not possibly be performed in the future under</p>	<p>Not accepted. Dose constraints have not changed.</p> <p>Code contains dose constraints not limits. HRECs determine whether research projects proceeds</p>

	<p>the proposed guidelines.</p> <p>The benefits of such research are tangible, demonstrable and measurable. The proposed guideline limits are based on a theory the co authors admit is not proven. The benefits of such limits are not based on tangible, demonstrable or measurable benefits to the subjects in question.</p> <p>The adoption of the proposed guidelines will seriously obstruct important, responsibly conducted medical research in this country which will have a negative impact on health care for Australians in the future.</p>	<p>Proposed dose constraints have been reviewed. Constraints apply to doses in addition to those administered as part of normal clinical management.</p>
<p><b>011</b> Doug Mackey Chairman, HURSOG</p>	<p>Members of HURSOG have reviewed the <i>Draft Code of Practice for Exposure of Human subjects to Ionising Radiation for Medical Research Purposes (2004)</i> and the associated RIS statement. Members wish to submit the following comments and suggested amendments for consideration by ARPANSA.</p> <p><b>Draft Code</b></p> <ol style="list-style-type: none"> <li>1. HURSOG welcomes the introduction of this <i>Code of Practice</i>. We believe that clear statements on reasonable research exposures will enhance the level of radiation protection afforded to subjects participating in research studies. NSW HURSOG members look forward to a working document in which researchers can easily find the information that they require to guide the safe formulation of their research and help them achieve success when writing submissions to ethics committees and regulatory bodies. We believe the NSW HURSOG guideline to have been a step in this direction and are encouraged by references to it in the Draft Code.</li> <li>2. The primary issue identified in the <i>Code of Practice</i> by NSW HURSOG members as requiring attention concerned the quantification of risk levels as presented in Annex 1.</li> </ol> <p>Members believe Annex 1 would be unsuitable to be used in a Patient Information Statement and Consent Form as the patient would be likely to believe that the risk is higher than the actual risk from the radiation exposure. The preferred terminology is that adopted by HURSOG in the Guideline <i>Research Protocols Using Ionizing Radiation in Human Volunteers</i>. This terminology was proposed by Professor Calman (UK</p>	<p>Annex 1 has been revised to incorporate Calman risk factors</p>

Chief Medical Officer) and published in BMJ 1996, 313:799-802.

Professor Calman's terminology uses the following scale:

Negligible	< 1:1,000,000
Minimal	between 1:100,000 and 1,000,000
very low	between 1:10,000 and 100,000
low	between 1:1,000 and 10,000
moderate	between 1:100 and 1,000

The HURSOG Guideline uses this terminology, together with the ICRP risk coefficient of  $5 \times 10^{-2}$  / Sv for the probability of fatal cancer in the general population (ICRP Publication 60), as follows:

<u>Terminology</u>	<u>Effective Dose range</u>
Negligible	< 20 $\mu$ Sv
Minimal	20 $\mu$ Sv to 200 $\mu$ Sv
very low	200 $\mu$ Sv to 2 mSv
low	2 mSv to 20 mSv
moderate	20 mSv to 200 mSv

An effective dose of 2-5 mSv, as found in many common radiological studies (eg lumbar spine x-ray, bone scan, head CT) would be classified as having an "intermediate level of risk" by Annex 1, but as having a "low level of risk" using the Calman terminology. Members believe that an "intermediate level of risk" is inappropriate for studies having a calculated risk of fatal cancer in the range 1:4000 - 1:10,000.

Members expressed concern about the use of a single composite value of risk without taking into account specific risk factors for sex, age and medical condition of the study cohort. Whilst these are approximately equal for older 'normal' volunteer subjects, they certainly do not apply for younger subjects. For example the risk factor for breast tissue in a teenage girl is ~ 14 x greater than for a 45 year old woman while the corresponding risk for a male in the same study would be much less. Similarly, does it really make sense to apply risk estimates derived for a

	<p>normal population to those who may have a very different prognosis?</p> <p>3. HURSOG members support standardization so that every researcher in every institution provides exactly the same information for the same risk factors. This would suggest a series of risk statements beginning with those for a normal average adult and then stratified by sex, age and medical condition that could be made available in an annex. It was felt that one of the strengths of the NSW guideline was the availability of standard risk statements.</p> <p>4. HURSOG members suggest that the Code of Practice should rely on the expertise of the ethics committees rather than the regulatory authority to determine that of the studies being performed for the trial, which studies are part of routine clinical management and which studies are additionally being performed as part of the research protocol. I.e. what studies are being performed beyond clinical management. For example if the sponsor decides to perform a CT or Nuclear Medicine study every 2 months instead of the normal 3 months.</p> <p>5. The guideline does not appear to address the issue of multi-centre clinical trials. Currently every hospital involved in a trial nationally has to go through the procedure of determining dose etc. Members consider it more sensible to have a uniform approach and wording for all participating centres which could be determined by a nominated centre who could then liaise with the other centres if required. This would also help the regulatory authority by reducing the volume of submissions which could perhaps be submitted as one by the sponsor. This could also be addressed in an Annex or Safety Guide.</p> <p>Members have reported to HURSOG the confusion arising when some sites have told the regulatory authorities about a multi-centre cancer trial and others haven't.</p> <p>6. Members point out that Paragraph 1.4 30 -33 can be construed to be an ambiguous statement. When research studies are performed, the radiopharmaceuticals used and medical devices employed are very often TGA approved for routine clinical use. Why should the code of practice NOT apply in the case of their application in research?</p>	<p>Agreed. Risk statements have been included in Annex 2</p> <p>Noted</p> <p>Advisory material added. Refer to Annex 3</p> <p>Regulatory authority involvement in dose assessment has been removed</p> <p>The revised scope and adoption into the NDRP should deal with this lack of uniformity</p> <p>Accepted. Sentence removed</p>
--	--	---

	<p>7. Paragraph 2.1.7 b) requires volunteers be excluded if past radiation history not verified – Members estimate it would be hard to implement without some statement as to what is meant by this.</p> <p>8. Members consider Paragraph 2.1.12 173,174 should not involve the regulatory authority as it should be an internal audit which the authority would expect. It should therefore read 'verification from a medical physicist'. Although Paragraph 2.12. a) to d) would put more responsibility on the medical physicist as it is hard to envisage the relevant regulatory authority having the resources to carry out these verifications.</p> <p>9. Annex 2 and Annex 3 repeat the same Table.</p> <p><b>RIS statement</b></p> <p>10. Members note that the RIS document (paras 62,68,69) refers in great detail to the HURSOG guideline but it is not referenced anywhere. Perhaps this is because it is not a legal document or officially published but it can be found on a website and should be included the RIS references. A published reference which covers most of the HURSOG guideline is:- Smart. R, Towson. J, Walker. B, Collins. L, Research protocols using ionising radiation in human volunteers – Communicating the risk to the volunteers : Proceedings of The 10th International Congress of The International Radiation Protection Association 2000, p 10-149.</p> <p>11. Members identified Items 10 – 18 as misleading because the considerable variation between the States in the number of projects using &gt;5 mSv could not be a true reflection of the research undertaken. For example in item 11 where 2 projects in Victoria used EDs&gt; 5 mSv. This would imply that there were only 2 projects in Victoria with CT scanning or Nuc Med studies, as the majority of those would routinely use &gt; 5 mSv. e.g. brain imaging. It also implies that cancer trials are probably not included.</p> <p>In comparison, Item 13 from South Australia, a much smaller state than either NSW or Victoria, seems more realistic with 7 projects with EDs&gt; 5 mSv. Item 12 compares Victoria to a single teaching hospital in NSW which alone had 8 projects over 3 yrs &gt; 5 mSv.</p> <p>It is clear that that these numbers should be identified as only representing</p>	<p>Accepted. Clause deleted.</p> <p>Accepted. Clause changed so that condition only applies to novel research and guidance material added to Annex 3</p> <p>Annex 2 removed</p> <p>Reference to HURSOG guidelines has been removed</p> <p>Reasons for the differences in the reporting to regulators are outlined in paragraphs 32, 41 and 42</p> <p>Additional statements will be added to emphasise this point</p>
--	---	--

	<p>the projects reported to the Authority, not as being the sum of all research projects done, which cannot be true.</p> <p>12. Members feel the RIS illustrates the confusion which exists as to what constitutes a reportable dose in cancer trial studies. This is reflected in Items 42 and 43.</p>	
<p><b>012</b> Jocelyn Towson, RPAH</p>	<p><b>General</b></p> <ul style="list-style-type: none"> <li>▪ The need for the Code is accepted</li> <li>▪ The Code blurs the distinction between the ‘research’ and the ‘exposure’. When evaluating a proposal, the HREC takes into account all foreseeable risks and benefits of the research. Only those risks related to the exposure should be the concern of this Code and the regulatory authority.</li> <li>▪ The main issue is the extended scope of the Code, which specifically covers radiological diagnostic studies used to monitor the outcome of therapeutic clinical trials. It is not clear whether clinical trials have to be referred to the regulatory authority if the dose from such diagnostic studies exceeds the Dose Constraints of Table 1, irrespective of whether the patient may derive a clinical benefit from the monitoring. The fact that it is the researcher’s responsibility to inform the regulatory authority before submitting the proposal to the HERC suggests that this is the case. The preferred alternative would be for the HREC to evaluate the clinical justification for the diagnostic studies and refer the proposal to the regulatory authority if it considered the exposure was not likely to benefit the subject and would exceed a Dose Constraint of Table 1. Otherwise, many clinical trials could be subject to significant delays and additional costs. It is not clear why the regulatory authority would want to review all clinical trials monitored with diagnostic radiological studies, unless it felt it had greater clinical expertise than the HREC.</li> <li>▪ The sponsor of a clinical trial should estimate dose, or acceptable range of doses, from proposed x-ray and nuclear medicine studies for review by the researcher/s and the institution/s where the research will be done. A dose range should cover different protocols and equipment, eg for CT scans.</li> <li>▪ Radiation dose estimates for diagnostic procedures may be generic ie. not specific to the individual subject. Risk assessment should be specific to the subject cohort, taking account of age, gender, state of health.</li> <li>▪ Dose estimates should be given for ED, maximum organ dose and uterus dose. For children and young adults, estimate dose to bone marrow, thyroid, gonads and breast tissue also.</li> </ul>	<p>Accepted Accepted. Distinction between radiation use in research and role of HREC has been emphasised through amended purpose and scope.</p> <p>Agree. Code currently agrees with this view. Additional advice in Annex.</p> <p>Agree. Code is consistent with this view. Further advice in annex.</p> <p>Information has been added to Annex 3</p>

	<p><b>Preferred review process:</b></p> <ul style="list-style-type: none"> <li>▪ Researcher obtains dosimetry report from Clinical Trial sponsor or a medical physicist (person accredited by professional organisation on or offshore, or approved by regulator) including details of dose calculation.</li> <li>▪ Researcher obtains information from the licensee on the QA program and measures to minimise dose and a statement that doses do not exceed Reference Levels where available.</li> <li>▪ Researcher includes the benefit of the research to society and the justification of the exposures including the risks/benefits to the subjects, in the submission to the HREC</li> <li>▪ HREC obtains advice from RSC, independent physicist or regulatory authority on the dose/risk report, the measures to minimise dose and the wording of the Participants Information Statement</li> <li>▪ HREC evaluates the justification for the exposure/s ie. risk v benefit, including: <ul style="list-style-type: none"> <li>- appropriateness, frequency and total no. of exposures</li> <li>- whether for monitoring possible adverse effects eg. reduced cardiac EF</li> <li>- whether for monitoring efficacy eg increased BMD</li> <li>- whether for normal control or placebo arm</li> </ul> </li> <li>▪ HREC advises researcher to refer proposal to regulatory authority if the exposures are not expected to benefit the subject in the view of the HREC's collective expertise AND the dose exceeds a dose constraint of Table 1. Regulator may wish to licence or accredit HRECs of, say, major hospitals to take on this responsibility.</li> <li>▪ HREC considers the advice of regulatory authority in approving or rejecting proposals.</li> <li>▪ Researcher includes radiation exposure/s in the annual and final reviews of project which it submits to HREC. 'Dose history' provided to subject and HREC could simply be researcher signing off the Information Statement to say the protocol was followed as described or as varied with a revised dose estimate.</li> <li>▪ HREC provides regulatory authority with a list of all radiation use proposals approved each year.</li> </ul> <p><b>Specific comments on Draft Code</b></p> <p><i>1.4 Scope</i>  24-26: Clarify whether procedures performed to monitor safety during clinical trials, ie. adverse outcomes, are regarded as 'normal clinical</p>	<p>Noted. Requirement for verification of dose has been added where doses are estimated to be in excess of constraints</p> <p>Independent medical physicist will now be used to verify information provided</p> <p>Accepted. Clause 1.4 changed to clarify.</p>
--	--	---

	<p>management’ 30-33 inconsistent with 21-23: Diagnostic radiology and nuclear medicine procedures use devices and radiopharmaceuticals approved by TGA</p> <p>2.1.2(b) 79-80: Very useful, in asking researcher to justify the exposures</p> <p>2.1.2(d) 83: Concept of the ‘relevant’ organ dose is not explained. Add to Glossary</p> <p>2.1.2(e) 86-87: Benefits. Change to ‘ the anticipated benefits that might reasonably be expected to result to society from the research as advised in Annex 1, and the benefits, if any, to the subjects from the exposure’</p> <p>2.1.2(f) This information should be obtained by the researcher from the licensee or Head of Dept where exposures are given</p> <p>2.1.2(g) This information should be obtained by researcher in consultation with the licensee or Head of Dept where exposures are given, and in particular that Reference Levels will not be exceeded.</p> <p>2.1.2(i) 101-102: Review of radiation doses. The preferred arrangement would be for ‘Exception reporting’ only, with the researcher to sign off the Participant Information Statement if the study was conducted as described with the dose estimate as given, or noting any variations - eg errors/omissions/additions to exposures - with a revised dose estimate, and keep a copy. It would be an impossible task to retrospectively calculate individualised dose estimates for all exposures for each subject.</p> <p>2.1.3(b) 127-128: no mention of how dose to fetus is “taken into account”. A possible dose constraint would be 0.1mSv, as for paediatric exposures for 12mths from conception in Table 1. A lower constraint would not be practicable because of limited accuracy of dose estimation for many procedures. 129-131: at beginning of study but not necessarily before every exposure?</p>	<p>Accepted. Lines 30-33 deleted.</p> <p>Acknowledged</p> <p>Accepted. Sentence clarified</p> <p>Deleted. Covered by NHMRC National Statement and not specific to use of radiation alone.</p> <p>Accepted. Advisory material added in annex.</p> <p>Accepted. Advisory material added in annex.</p> <p>Agree. Clarified with amendment to scope so that novel uses of radiation are covered</p> <p>Accepted and amended with insertion of new clause</p> <p>Noted. Before every exposure where status is uncertain.</p>
--	--	---

	<p>NB clinical trials usually exclude pregnant women. As a guide, need for pregnancy testing (urine test sufficient) in women of reproductive capacity could be related to equivalent dose to uterus:</p> <ul style="list-style-type: none"> <li>- not required if uterus dose is less than 0.1mSv</li> <li>- at discretion of licensed physician if uterus dose is between 0.1mSv and 1mSv</li> <li>- mandatory if uterus dose is above 1mSv.</li> </ul> <p>2.1.4 138: Change “research” to “exposure”</p> <p>2.1.5 142: Change “parent or guardian” to “parents or guardians” 144: Change “research” to “exposure”</p> <p>2.1.7(a) Too restrictive. Not necessary if subjects have participated in very low dose studies in the past eg. BMD. Goes beyond the meaning of ICRP62 (56) which says “In general it is undesirable for the same individual to repeatedly take part in investigations involving exposure to radiation and ethical committees should ascertain that this is not occurring <i>inadvertently</i>.”</p> <p>2.1.7(b) Insert “from research studies” after “radiation history”, as clinical exposures are irrelevant and no one can tell you how much dose they’ve had.</p> <p>2.1.7(c) Insert “and not more than the relevant Reference Levels” after “practicable”</p> <p>2.1.7(d) Estimating absorbed dose to skin from multiple CTs or prolonged fluoroscopy could be problematic, given the large no. of clinical trials and the minute number of radiology physicists. Calculators like ImPACT are helpful for CT.</p> <p>2.1.9 According to the Scope of the Code, this clause implies that researchers will have to obtain advice from the regulatory authority for all clinical trials</p>	<p>Footnote 2 amended to become part of new sub-clause. Noted Noted advisory material added to annexes</p> <p>Noted. Additional clause inserted</p> <p>Accepted</p> <p>Not accepted Accepted</p> <p>Moved to advisory material in annexes</p> <p>Include further advice in annexes</p> <p>Moving clause to annex</p> <p>Changed so that assessment is obtained from medical physicist</p>
--	---	---

	<p>monitored with nuclear medicine or x-rays except BMD, even if the procedures are done for safety reasons.</p> <p><i>2.1.10</i> The prospective estimates of dose should be sufficient, except where there has been a change to the intended protocol. See 2.1.2(i)</p> <p><i>2.1.12(b,c)</i> Are all regulatory authorities going to be prepared to verify QA status of departments, and procedures which will be followed to minimise dose? These assurances should be obtained from the licensees.</p> <p><i>2.1.13</i> Include a time limit of 5 years, beyond which it is not necessary to show the dose record (ie. the signed off Participant Information Statement) to future researchers.</p> <p><i>2.2.2</i> 'Parent' and 'guardian' should be plural if appropriate.</p> <p><i>2.5</i> The role of the regulatory authority is to advise the researcher when the researcher must seek advice of the regulatory authority. Circular argument? The regulatory authority will simply adopt this Code from the National Directory. The Code says all clinical trials over the dose constraints of Table 1 have to be referred to the regulator. Table 1 dose constraints only apply where no benefit to the exposed person is expected. Should it be left to the researcher or to the HREC or to the regulatory authority to rule on what studies are in excess of the subject's clinical needs?</p> <p><i>3</i> 259-260: The quantity Equivalent Dose is an average for the whole organ, except in the case of skin. A dose constraint to a portion of an organ would have to be in grays, but would be very hard to establish. Dosimetry report should include: dose to organ or tissue that gets maximum dose, dose to uterus, effective dose. For children, research exposures are only intended for a medical condition, not healthy subjects. A dose constraint of 0.5mSv in any year may be difficult to achieve, eg respiratory studies in asthma or cystic fibrosis, so most studies</p>	<p>Clause removed as this is covered in the NHMRC National Statement</p> <p>Verification of dose and risk assessments will be undertaken by an independent medical physicist</p> <p>Removed. Covered by amended clause 2.1.3</p> <p>Condition removed as it is covered in clause 2.1 or NHMRC National Statement</p> <p>Regulatory authority role has been replaced with independent medical physicist. HREC has responsibility for justified use of radiation. Advice on optimisation has been included in the Annexes</p> <p>Reference to 'portion of organ' has been deleted.</p>
--	--	--

	<p>will be referred to regulatory authority. Organ dose of 200mSv was derived for skin, eyes but sounds high for other organs. 265-268: footnote (a) suggests that Table 1 only applies to subjects who do not themselves benefit from the exposure. See above.</p> <p><i>Annex 1</i> 280-308: After explaining that risk averaged over the full age distribution can be estimated from effective dose, this adaptation of ICRP62 does not quite make clear how the table was prepared – refer to para (52). The ICRP started from perceived levels of risk and worked back to a corresponding effective dose in a population of “normal average adults”, not the whole population. Caption should maybe “Categories of risk and corresponding levels of dose to adults and benefits to society”</p> <p>ICRP(1993) should be ICRP(1991) – Publication 62. Also in reference list.</p> <p>337-340: Sounds odd to find background radiation assigned to Category III levels, are extreme radon levels applicable in an Australian Code?</p>	<p>Clarified through addition of Table 2 to Annex 1 which reflects age and sex distribution</p> <p>Noted and reference amended</p> <p>Agreed. Clause deleted</p>
<p><b>013</b> Dr Graeme Dickie Faculty of Radiation Oncology RANZCR</p>	<p>In general ARPANSA is to be congratulated on this document that in many respects makes the guidelines for the use of radiation, particularly the use of diagnostic radiation clearer. The guidelines on the use of radiation, particularly the restrictions in children and in pregnancy are endorsed.</p> <p><i>Line 263 table 1</i> While the terms and doses of “effective dose” and “equivalent dose” are appropriate and are taken from ARPANSA 2002, these are quite confusing terms to a person from a Research Ethics Committee. Unfortunately, those terms have the same units “mSv” but are quite different. Why those terms should have such an apparent wide difference in dose is hard to understand. Although those terms are listed in the glossary, the definitions are too brief. I suggest it is necessary to expand on the definitions.</p> <p>Line 255- 258 “...the cumulative effective dose to adults and children must conform with the dose constraints as tabulated below unless the Human Research Ethics Committee is provided with specific advice approval from the relevant regulatory authority to exceed these dose constraint.”</p>	<p>Agreed</p>

	<p>Line 272 similar statement to above</p> <p>These above statements create significant problems with respect to radiotherapy research. All radiotherapy treatments exceed these constraints. As this statement stands it is mandatory for all radiotherapy research proposals to be referred to the regulatory authority. In most research proposals that involve radiotherapy, the radiotherapy may be standard treatment but the research question may involve giving radiation with or without a drug. We do not see any reason why the regulatory authority should be involved in such a research proposal.</p> <p>The requirement to submit all radiotherapy research proposals to a regulatory authority is unnecessary, restrictive, creates extra work and is likely to be a disincentive to research in the radiotherapy area. It would seem that the sentiment of the document is to limit radiation which would normally not be used in medical practice but in doing so it has created a situation which is very restrictive (and in my opinion unnecessarily so) for research in radiotherapy.</p> <p><i>Line 580</i> Glossary</p> <p><i>Line 583 (see Annex B)</i> – there is no Annex B</p> <p><i>Line 634-637 (see Annex B)</i> – there is no Annex B As indicated above cumulative effective dose should be defined</p> <p><i>Line 643 -645 (see Annex B)</i> – there is no Annex B As indicated above cumulative equivalent dose should be defined</p> <p><i>Line 765</i> International Commission on (not for) radiological protection</p> <p><i>Line 768</i> International Commission on (not for) radiological protection</p> <p><i>Line 781</i> Royal Australian and New Zealand College of Radiologists (RANZCR)</p>	<p>Regulatory authority involvement has been replaced with verification by a second medical radiation physicist</p> <p>Requirement removed.</p> <p>Annex B is in RPS 1 and contains quantities used in radiation protection Annex B is in RPS 1</p> <p>Annex B is in RPS 1</p> <p>Correction made</p> <p>Correction made</p> <p>Correction made</p>
<p><b>014</b> Brenda Walker MSc</p>	<p><b>1)</b> I think the statement ... <i>'the researcher must keep the radiation dose to subjects to the minimum level practicable'</i> ... has been misinterpreted</p>	<p>Agreed</p>

<p>Principal Physicist Dept. of Nuclear Medicine Prince of Wales Hospital</p>	<p>I read this as referring to either the number of radiation studies done on a patient in the study or the possibility of reducing the actual dose given. eg. in a clinical trial the sponsor may want to do a CT/MUGA every 2 months on a patient when every 3 months would be adequate. I do not think this refers to the technical aspect. 2.1.7 is referring to the researcher's requirement before the study proceeds and is accepted by the HREC and I believe is quite acceptable.</p> <p>2.1.7(c not b) lines 154-155 Typically it is not the responsibility of the researcher to keep the radiation dose to the human subjects to the minimum level, it is the responsibility of the operator of the equipment or the physician prescribing the radiation dose to ensure this. In most instances the researchers request an ionizing radiation procedure to be conducted and this is performed by radiology, nuclear medicine or radiotherapy personnel. The keeping of the doses to the minimum level should be in keeping with their normal good practices (see relevant COPs).</p> <p>2) I do not understand this response. The researcher has to add up (ie. assess) all the doses being given to any one subject in the research study and if it is over the limits then he has to advise the regulatory authority. In NSW this is on the form for EPA. I have no problem with this clause but agree with the ACPSEM 2nd sentence that the reasons for going over the limits must be stated.</p> <p>2.1.8 lines 160-161 From a regulatory perspective it is impossible to evaluate and enforce if a researcher has '&gt; assessed&gt; &gt;' whether the cumulative dose has exceeded the dose constraints. That point aside, a clear statement as to why the dose constraints cannot be met and the implications for the project should be required.</p> <p>3) I do not agree with these statements. In NSW the letter of acceptance from the regulatory authority accompanies the hospital radiation safety committee approval to the HREC. It would be wrong for Ethics to approve a project without this. They are often done concurrently, HREC approving on the condition that the authority has approved. I do not think the 2 sections should be combined but I think 2.1.12 should remove 'authorisation from regulatory authority' and leave 'verification from a medical physicist' as list a) to f) is a local issue which is required of the regulatory authority but</p>	<p>Noted and included in Annex 3</p> <p>Agree</p> <p>Regulatory requirement is that accurate information is provided to HREC and participants. Assessment of dose is undertaken by medical physicist(s).</p> <p>Agree</p>
---	--	---

	<p>should not have to be checked by them.</p> <p>2.1.9 lines 162-165 This seems to be placing much more onus on the Regulator than is currently the case in Victoria, at least, since normally research protocols are only submitted for regulatory review &gt; after they have received approval of the HREC. Is that the intention? Possibly the two sections 2.1.9 &amp; 2.1.12 should be combined.</p> <p>3. Lines 254 - 262 This statement is a little bit ambiguous and tends to imply that approval from the regulatory authority is required prior to the HREC giving approval. Vis-à-Vis 2.1.9 lines 162-165, and, 2.3.2 (d) lines 224 - 227. Also refer to 2.3.3 in which it states that the HREC has assessed and considered the radiation related risks of the research. The implication is that this done prior to it being submitted to the relevant regulatory authority.</p> <p>It is obvious from the comments that different States do things differently and hopefully this will be resolved by this COP.</p> <p>4) I disagree with this statement. I think 2.1.13 is important for legal reasons and I would envisage a signed copy being kept by the researcher as well. The information would be on the consent form that the patient signs so this could be used. If the subject loses it that is then their responsibility.</p> <p>2.1.13 lines 188-191 If this is expected to ensure that past history of exposure will be kept then it is doomed to failure. Most people can &gt; &gt; t even keep/find previous films in many cases as it is now. They would have even less chance of retaining paper records or remembering if or when they have undergone radiological procedures.</p> <p>I do not think the issue of what constitutes a reportable dose eg in clinical trials, is very clearly spelled out in the new guideline although it is stated in 1.4 SCOPE. 21-23. I think the safety guide as recommended by ACPSEM could perhaps provide an example or a questionnaire for the researcher on how to determine what constitutes a reportable dose (particularly relevant to clinical trials)</p> <p><b>Code of Practice</b></p> <p>I feel that one of the most important aspects of the Code is that it is 'user</p>	<p>Regulator role in dose assessment has been replaced with independent medical physicist</p> <p>Process has been changed</p> <p>Noted</p> <p>The obligation is limited to the researcher having to advise the participant to retain the records</p> <p>Noted. The National Statement on Ethical Conduct in Research Involving Humans contains requirements for record keeping. The Code contains advice that participants keep records in accordance with Table 1 however difficulty in ensuring compliance is acknowledged.</p> <p>Accepted and clarified in Annex</p>
--	---	--

	<p>friendly' to the Researchers so that they are encouraged to follow it and there are no ambiguities. I therefore support the idea of a Safety Guide or Annex with the practical issues addressed. Eg.</p> <p>a) I believe it is essential to provide standard risk statements which can be inserted into the patient information/consent forms. This means that every researcher nationally will provide the same information to the patient. This has not been provided in the COP although Part 3 describes the categories of risk. The HURSOG guidelines, which are referred to in the RIS on several occasions, provide these statements and I believe researchers in NSW have found them very useful.</p> <p>b) I believe there should be a guide on determination of what constitutes a reportable dose in a clinical trial ie. what studies are being performed beyond routine clinical management eg. if the trial sponsor decides to do extra CT/Nuc Med studies. I do not feel the guideline as it stands is clear enough on this issue although it was addressed in the RIS.</p> <p>c) Unfortunately the guideline does not appear to address the issue of multicentre clinical trials. Currently every hospital involved in a trial nationally has to go through the procedure of determining dose etc. It would be so much more sensible to have a united approach and wording by all participating centres which could be carried out by a nominated centre who could liaise with the other centres if required. This would also help the regulatory authority by reducing the amount of submissions as it could perhaps be an obligation of the sponsor to provide all the data.</p> <p><b>Section issues</b></p> <p><b>1.4 30 – 33.</b> I find this a very ambiguous statement as obviously we are using TGA approved radiopharmaceuticals for research studies.</p> <p><b>2.1.2 83,84</b> What is the definition of a 'relevant organ'?</p> <p><b>2.1.12 173,174</b> I feel should not involve the regulatory authority as it would be an internal audit within the hospital which the Authority would expect to be carried out. It should therefore read 'verification by a medical physicist'.</p> <p><b>2.3</b> I support this section as I believe the Human Research Ethics Committee must see the statements/requirements from the Regulatory Authority before accepting the proposal. This is the order of things in NSW but it would appear</p>	<p>Agreed</p> <p>Standard risk statements have been included in the annex</p> <p>HURSOG guidelines incorporated in Annex 2</p> <p>The scope has been modified to apply to exposures that are in addition to those received as part of normal clinical management</p> <p>Guidance provided in Annex 3</p> <p>The involvement of the reg authority in the approval process has been removed</p> <p>Accepted. Clauses deleted</p> <p>Accepted. Wording altered</p> <p>Accepted</p> <p>Noted</p>
--	--	--

	<p>not to be the case in Victoria.</p> <p><b>RIS</b></p> <p>a) The HURSOG guidelines are referred to several times (eg. 62, 67, 68) but are not referenced. I feel this is unacceptable. Dr. Smart can provide a publication reference or a reference to an Internet site could be given.</p> <p>b) Items 10 – 18 are misleading comparisons as the implication is that these were the only research studies carried out in the different States. I believe that they refer instead to the studies reported to the authorities only. It would be very surprising if in Victoria in 2002 there were only 2 projects with EDs &gt; 5 mSv as any project involving a CT or a Nuc Med brain scan for example would give doses higher than 5 mSv.</p>	<p>Reference to be included</p> <p>Additional statement will be included clarifying that not all relevant research projects in Victoria are referred to the regulator due to ambiguity in the RHS12 due to the differences outlined in paragraphs 42 &amp; 43</p>
<p><b>015</b> Dr Greg King The Woolcock Institute of Medical Research , Royal North Shore Hospital, St Leonards</p>	<p><b>Line 82.</b> When available (for those services when there is insufficient manpower which could easily happen if they have to do every single study that need imaging of some sort), The Radiation Safety Officer of the local area health services should oversee the documentation that is required for approval including the written report of the estimate of radiation dose from a medical physicist and Subject Information Statements. This would seem appropriate since the Officer is usually a medical physicist.</p> <p><b>Line 325.</b> There is a disparity between Categories IIa and IIb and the apparent level of risk perceived by some Radiation Safety Committees and the information in Table 1, with respect to the level at which a minor level of risk should be set. Category IIa would be better set at 0.1 to 5 mSv. This part seems confusing also, eg what does 10-6 refer to (table) and also line 311 "risk in the order of ..." is this risk of fatal radiation cancer ?? should be defined. Same for 325, 330, 335 Perhaps It should be categories as follows:- I minor II (whether it be 0.1-5 or 0.1-1) intermediate III moderate IV substantial</p> <p>In <b>annex 1</b>, the vague statement that 0.1mSv is the natural background radiation in a few weeks could perhaps be expanded to give a range for the various parts of Australia as there may be known differences or at least a</p>	<p>Noted. Method for compliance rather than requirement.</p> <p>Table has been amended in accordance with Calman terminology</p>

	<p>reference provided for local Stakeholders to investigate.</p> <p>Also for <b>Annex 1</b>, reference is made to the level of societal benefit, which ranges to knowledge increment only to saving of life. One would be concerned that these are generic statements and do not provide guidance to HRECs eg. lung cancer CT screening may benefit (if proven) the very few sub % of curable screen detected cancers but may cause risk to many healthy others compared to investigation of a flourosopic research with a new coronary stent which may potentially mitigate serious disease in a much larger proportion of people, each of whom already has proven coronary disease. There needs to be tighter definitions, and a formal evaluation guideline to help assess societal impact of research ala EBM type assessment of quality.</p> <p>In <b>annex 2</b>, there should perhaps be some explanation of effective dose vs absorbed vs equivalent dose (apart from the brief description in glossary) to guide HRECs and researchers. Furthermore if footnote 3 line 356 is not recommended in Australia it should not be included.</p> <p>Moreover, annual Equivalent doses for all the other major organs eg heart, lung etc should be given for researchers working specifically in those areas or at least a link to the accepted publication of aforementioned.</p> <p><b>Annex3</b> Lines 452 to 470 appear to be repetitive and superfluous following Annex 2.</p> <p><b>Page 4. Footnote.</b> The requirement for a serum pregnancy test prior to the radiation exposure is not useful if there is no maximum time between serum pregnancy test and the radiation exposure specified. Documentation of the use of adequate contraception and last sexual intercourse on the day of radiation exposure would be easier, more practical and sufficiently sensitive for diagnosing unexpected pregnancy.</p> <p>In this regard, given the LNT hypothesis, is any radiation (research) dose justifiable to pregnant women???? - probably but the ethics should at least be considered for the unborn child who has no knowledge or control over dose received ala drug trials in pregnant women..</p>	<p>Footnote amended to accommodate and turned into new clause which indicates test is immediately before exposure to radiation.</p> <p>Yes because some dose to fetus is minimal. Clause added to clarify</p>
--	--	---

	<p><b>Glossary</b> - refers to the Annexes as "B" etc whereas they are actually numbered.</p> <p>Consumer - there should be a de-jargonised consumer version that should be made available for potential research subjects.</p>	<p>Annex B is in RPS 1 and contains quantities used in radiation protection</p> <p>This has been taken into account in development of risk statements</p>
<p><b>016</b> Mike Carter</p>	<p><b>General Comments</b></p> <p><b>What are the benchmarks for the constraints on volunteer exposures?</b></p> <p>There seems to be an ethical/philosophical question that this draft Code does not address but which is important to the topic that it addresses.</p> <p>It is important that recommended dose limits or constraints are reasonably consistent one with another. The main benchmarks to which any recommended limit or constraint will be compared are the natural background and the ICRP recommended limits. If limits or constraints are proposed that are significantly less than the variation in natural background they lose credibility because we do not take any action to reduce or control natural background other than radon in houses. If limits or constraints are proposed that are significantly less than the ICRP values, ICRP loses credibility for proposing values are dangerously high. (Unfortunately the ICRP is not itself always internally consistent).</p> <p><b>Who are the volunteers?</b></p> <p>This draft Code applies to two distinct groups of people.</p> <p>One group are patients already suffering from some disease who are asked to volunteer to take part in testing a procedure that may result in a better understanding and more effective treatment of the disease. These volunteers could have some personal gain from the procedure being tested. In addition they may have a limited life expectancy.</p> <p>The second group are healthy individuals who volunteer to assist the project. They have nothing to gain from taking part in the project.</p> <p>The draft Code does not clearly address the fact that there are two distinct groups. An argument could be made for a higher dose constraint for the first group than that for the second group. I am not proposing that this should necessarily be the case but that it should be discussed in the draft Code. (It is implied, in passing, in footnote a to Table 1 and in Annex 1, that patient</p>	<p>Ethical issues associated with research of this type is covered by the National Statement on Ethical Conduct in Research Involving Humans which is administered by the HREC</p> <p>Values chosen are consistent with 2005 draft recommendations of ICRP (paragraph 226)</p> <p>The scope of the code has been clarified to include exposures that are in addition to normal clinical management. This removes the question of whether there is medical benefit or not</p> <p>The aim of the Code is to ensure HREC and participants are provided with accurate and correct information on which to base their decisions which require that non-radiation factors also be taken into account</p>

volunteers could be subject to a different constraint, but this should be clarified).

**Detailed comments**

**Dose constraints. Table 1**

In Table 1 on page 9, what is the value of setting an organ dose limit of 200 mSv? Tissue weighting factors range from 0.01 (skin and bone surface) to 0.2 (gonads). Thus the effective dose due to a 200 mSv organ dose could range from 2 mSv to 40 mSv. If the latter then it would be unacceptable as it exceeds the annual effective dose constraint. For most organs the effective dose from an organ dose of 200 mSv would be 24 mSv, which also exceeds the annual effective dose constraint. Should this limit be changed to one or two specific organs or should the generic organ dose be changed?

A second point that should be borne in mind is that the occupational and public dose limits recommended by the ICRP include a dose and dose rate facto (DDRF) of 2. Literature suggests a range of DDRFs up to 10. Thus the organ exposure of 200 mSv quoted in the Table, if it is a short term exposure as it presumably is, would represent the same risk as a long-term exposure of between 400 and 2000 mSv. The ICRP has not, as far as I am aware, indicated what it means by short-term exposures. DDRFs are mentioned in Annex 3 but it is not clear if, or how they have been used in setting the dose constraints.

In addition, in Table 1, I question the practicality of setting 5-year cumulative dose constraints unless we have a good national registry of exposures to volunteers, which I suspect we do not have at present. You cannot depend on the volunteer to keep and provide a record to another hospital possibly in another State. In addition, for cumulative doses, again the question would arise as to whether or not to apply a DDRF for a fractionated exposure over several years.

**Categories of risk Table, page 10**

The public limit is an average of 1 mSv per year above natural background with no year being greater than 5 mSv. This in itself presents a credibility problem in that the natural background varies from slightly less than 2 to about 10 mSv per year. (In a few areas it is around 20 mSv per year but I don't want base my argument on a few special cases). This means that, depending on where you live, how your house is designed and your lifestyle; your total

For most organs, effective dose is limiting factor, except in the case of skin. It is possible for a small area of skin to receive high doses even though the rest of the body does not.

ICRP definition for doses to skin includes averaging over 1 cm<sup>2</sup>

Noted

	<p>annual average acceptable dose could be 3 mSv or 11 mSv. We make no attempt to control public dose by preventing people from living for long periods in known high background dose areas. Neither do we try to control the dose of regular frequent flyers from Australia to Europe. In theory both of these forms of higher than normal exposure could be controlled. In practice it would not be economically or socially acceptable to do so.</p> <p>Thus an annual dose of 1 to 10 mSv from natural sources to a limited number of people is treated as a trivial exposure. I therefore have a problem with this Table, which regards this dose range to have a risk that is minor to intermediate. The “acceptable” exposure from radon in houses is in this range. I suggest that the table used by HURSOG is adopted but with the “negligible” and “minimal” categories combined. It becomes very difficult to explain to the public why we take no action when they may be receiving 5 or more mSv per year from natural sources but express concern when they receive an additional 0.5 mSv per year from a “practice”.</p> <p>It would be useful to explain the levels of societal benefit more clearly. The users of this Code would not necessarily have access to ICRP publications.</p> <p><b>Glossary</b> I suggest that only terms used in the draft Code are included in the Glossary.</p>	<p>Accepted and included in Annex 2</p> <p>Noted</p>
<p><b>017</b> LD Oliver President Australasian College of Physical Scientists and Engineers in Medicine</p>	<p>Firstly we note the three options outlined in the RIS statement and support the contention that option 3 is the only viable choice. A replacement for the NHMRC Recommendations of 1984 is essential. To do nothing is not acceptable and allowing researchers to produce their own ground rules under which they would operate would lead to a fragmented, inconsistent, potentially hazardous and generally unacceptable outcome.</p> <p>Essentially, the ACPSEM has found the document to be a useful document but we do have a number of suggestions. Individual members, who have considerable expertise and experience in radiation protection as applied to medicine, have provided a number of comments and suggestions that would improve the document or make it more useful to the potential stake holders.</p> <p>Firstly, a general point about what we regard as an important omission. We would like to think that this document provides an ideal opportunity to make a major step towards achieving national uniformity in matters of research</p>	<p>Noted</p>

	<p>involving ionizing radiation. Accordingly, we believe that the document should provide model risk statements that all researchers, regardless of location might employ. We would even suggest that the HURSOG (NSW) risk statements, modified in late 2003, might provide a very suitable starting point for these.</p> <p>We also are of the opinion that the COP needs to have an accompanying Safety Guide in which advisory statements are made. At present the document would be a Regulatory nightmare to implement since it mixes mandatory requirements (must) with advisory requirements (should). Indeed, some of our own suggestions fall into the advisory category rather than mandatory and would be better placed in a Safety Guide. To enable Regulatory enforcement there must be a clear distinction between mandatory and advisory statements.</p> <p>Other specific comments about the draft are summarised in table form below.</p> <p><b>Page 1</b> <b>Clause 1.4</b></p> <p>The scope describes where this COP applies but curiously does not use the term volunteer at any point. Surely, we are talking about individuals volunteering to take part in trials and the term should be used.</p> <p>While we fully realise the difficulties in defining who and when individuals are classified as volunteers it is an issue of central importance that must be addressed in this document.</p> <p>Having grappled with trying to find a universal definition of volunteer it may be more useful to define one by exclusion, ie. Define who is a patient and anyone who does not fit that definition is by exclusion a volunteer and that project shall be referred to the regulator.</p> <p><b>1.4 lines 15-17 &amp; 19-21</b></p> <p>In the PURPOSE it refers to ‘human subjects’ whereas in the SCOPE it refers to ‘human research subjects’. In addition, the document then only refers to these volunteers as ‘subjects’. The terminology needs to be consistent throughout the document.</p> <p><b>1.4 lines 19-23</b></p> <p>The document really needs to define ‘a medical benefit’. From experience the term medical benefit has been open to interpretation. Researchers have commonly quoted that ‘knowing the results from a DEXA scan or a chest</p>	<p>Agreed. Model statements included in annex</p> <p>Agreed. Advisory material added</p> <p>Not accepted because patients can be volunteers in research</p> <p>Definition of research participant in glossary and as used in the National Statement</p> <p>Using participant</p> <p>The use of additional radiation is considered more important. Reference to ‘medical benefit’ removed and the definition focussed on additional radiation.</p>
--	---	---

	<p>radiograph being reported on' is a medical benefit. From a radiation protection point of view this is not the case and hence the term medical benefit needs to be put into context. This should ideally occur in a Safety Guide.</p> <p><b>1.4 lines 30-32</b></p> <p>In line 30, reference is made to the code covering "novel procedures". What does this mean in a therapy setting? Does it mean new treatment modalities such as High Dose Rate (HDR) brachytherapy, Intensity Modulated Radiotherapy (IMRT), intra-operative therapy, conformal stereotactic therapy, etc? Some sort of definition would be good.</p> <p>What about dose escalation studies? What about repeat or extra CT, PET, MRI scans for therapy purposes, in a clinical trial?</p> <p>Also, greater clarification is needed re the non-applicability of the risk-benefit categories to therapy trials. Below is the sort of statement usually appended to the RSO reports on research proposals at Peter Mac:</p> <p>“With regard to the risk level categories in module 5 (DHS document), these are derived from the International Commission on Radiological Protection, Publication 62, Radiological Protection in Biomedical Research (1993). Reference to this publication makes it clear that the risk levels are intended to be applied when low levels of radiation are given to healthy subjects, where the risk needs to be balanced against the possible benefit to society. For patients undergoing radiotherapy, the dose received is many orders of magnitude higher, but the potential benefit to the patient (cure or control of their disease) justifies the risk. It is not meaningful to assign a risk level category as per module 5. The radiation oncologist prescribes an appropriate dose to give a high probability of tumour control and a low probability of radiation-induced complications. For this study, the 5 Gy given as a single dose intraoperatively is considered to be radiobiologically equivalent to 10 Gy in five fractions which would otherwise be given as an external beam boost after radiotherapy to the whole breast. Therefore, as for all radiotherapy prescriptions, the anticipated benefit to patients who participate in the study justifies the possible side effects.</p> <p>Some similar statement in this document would be good.</p> <p>Why does this COP not apply to pharmaceuticals (radiopharmaceuticals?) or medical devices approved by the TGA? Surely, if the use of such approved</p>	<p>Clarified in scope</p> <p>Would be subject to the code</p> <p>Accepted. Further advice provided in annexes</p> <p>Scope has been modified to apply to exposures in addition to that received as part of normal clinical management of patients</p> <p>Agree. Reference deleted</p>
--	---	---

	<p>devices and pharmaceuticals is above and beyond normal clinical practice (e.g. the research trial requires an additional CT scan on a TGA approved device to be performed) then such exposure must be subject to this COP.</p> <p><b>1.4 line 39</b> The role and responsibility of a “researcher” is outlined. We suggest that this should be the role and responsibility of the “principal researcher”. To require all researchers to have this role is draconian and would create enormous unnecessary paperwork. Adoption of this suggestion would require changes throughout the document and in the Glossary.</p> <p><b>Page 4</b> <b>2.1.1(a): lines 68 – 70</b> This requirement is redundant based on the requirement of 2.1.1(c). In order for somebody to comply with the regulatory requirements they must have already considered them. In addition, from a regulatory perspective it would be impossible to evaluate and enforce this.</p> <p><b>2.1.2(b) lines 79 &amp; 80</b> Preferred text: ‘ <i>the justification for exposing human subjects to ionizing radiation for the purpose of the research;</i>’</p> <p><b>2.1.2(b) lines 82-85</b> The sub-clause should also require the estimation of the maximum absorbed dose to the skin averaged over any 1 cm<sup>2</sup>, where relevant (this item is referenced further in the document in Section 2.1.7(d))</p> <p><b>2.1.2(i): lines 101-102</b> Whilst this is a highly commendable ideal we have concerns that this may not be easy to achieve. Additionally, it is not clear whether it is the intention that indicative dose records are to be kept or individual doses are to be kept. The latter would create an even greater administrative nightmare. This sub-clause and 2.1.10 also have overlap.</p> <p><b>2.1.3 (a)(iii) lines 116 &amp; 117</b> The document uses the term health or medical authority. The term should be replaced with ‘relevant regulatory authority’ for consistency.</p> <p><b>2.1.3 (a)(iii) line 117</b></p>	<p>It is implied that the principal researcher is that putting forth the research proposal</p> <p>Accepted</p> <p>Not accepted. Existing wording encourages justification of the use of radiation over other means rather than just amount of radiation</p> <p>Not accepted. The Code should be broad with respect to this.</p> <p>Accepted. Focus on novel uses of radiation. Change to clause</p> <p>Clause deleted</p>
--	--	---

	<p>The document states ‘with the permission of the parents’ should be replaced with the term ‘with the permission of the legal guardian’.</p> <p><b>2.1.3 (b)(i) line 122</b> The word ‘problems’ should be replaced with the word ‘conditions’.</p> <p><b>2.1.3 (b)(ii) line 126</b> It only became apparent from further reading of the document what was meant by ‘and the risks are minimal’. This statement should quote/reference Annex 1.</p> <p><b>Page 5</b> <b>2.1.4: lines 136-139</b> We believe this is where reference should be made to suitable model risk statements. Perhaps the risk statements should be referred to at this point and included as an Appendix, Annex or better still in a Safety Guide. The risk statements should have some comparative risk values in them so that the participant can gain some sense of the magnitude of the risk. Any ‘associated risks’ should be in a form that is easily understood by the volunteer and compares the risk to risks associated with every day events. (For example see IRPA Proceedings P-10-149 Research Protocols using Ionising Radiation in Human Volunteers - Communicating the Risk to the Volunteers (R.C. Smart, J.E. Towson, B. Walker and L. Collins))</p> <p><b>2.1.5 line 141</b> ‘including the case of irradiation of a child’ is redundant. Children are never in a position to give informed consent and hence this is covered by the preceding statement (line 140).</p> <p><b>2.1.7(b) lines 154-155</b> Typically it is not the responsibility of the researcher to keep the radiation dose to the human subjects to the minimum level, it is the responsibility of the operator of the equipment or the physician prescribing the radiation dose to ensure this. In most instances the researchers request an ionizing radiation procedure to be conducted and this is performed by radiology, nuclear medicine or radiotherapy personnel. The keeping of the doses to the minimum level should be in keeping with their normal good practices (see relevant COPs).</p>	<p>Clause deleted</p> <p>Accepted</p> <p>Accepted and clause amended</p> <p>Agreed. Included in annexes</p> <p>Not accepted</p> <p>Acknowledge with additional advice regarding optimisation in the annexes</p>
--	--	---

	<p><b>2.1.7(b) lines 152-153</b> Does this refer to all radiation history (medical &amp; occupational as well as research)? Why should it matter which it is? Again an administrative nightmare as recall of previous radiological history is dubious at best.</p> <p><b>2.1.7(d) lines 156-157</b> The estimate of skin dose should be to the maximum absorbed dose to any 1 cm<sup>2</sup>, not to the skin in general. Is it truly necessary to single out CT examinations? Perhaps CT fluoroscopy is an area for concern. The reference to fluoroscopy high dose rate should probably refer to “Boost mode”. Should we put it in terms of Deterministic Risk? We presume this is the issue. The ‘principal’ researcher must clearly document any exposure(s) that are likely to exceed and cause Deterministic effects/detriment.</p> <p><b>2.1.8 lines 160-161</b> From a regulatory perspective it is impossible to evaluate and enforce if a researcher has ‘assessed’ whether the cumulative dose has exceeded the dose constraints. That point aside, a clear statement as to why the dose constraints cannot be met and the implications for the project should be required.</p> <p><b>2.1.9 lines 162-165</b> This seems to be placing much more onus on the Regulator than is currently the case in Victoria, at least, since normally research protocols are only submitted for regulatory review <u>after</u> they have received approval of the HREC. Is that the intention? Possibly the two sections 2.1.9 &amp; 2.1.12 should be combined.</p> <p><b>2.1.10 lines 166-168</b> Suggest, for clarity, the text should be replaced with the following: <i>The research must ensure that the records of human subjects included consent forms; radiation dose records and details of the research undertaken are maintained.</i></p> <p><b>2.1.11 line 169</b> The word ‘research’ should be inserted before proposal.</p> <p><b>Page 6</b> <b>2.1.13 lines 188-191</b></p>	<p>Deleted</p> <p>Moved to annexes</p> <p>Requirement removed. Focus is now on validity of assessment by medical physicist</p> <p>Not accepted</p> <p>Clause amended. Clause 2.1.9 and 2.1.12 combined with emphasis on medical physicist.</p> <p>Requirement removed as it is applicable to all research and covered by the National Statement</p> <p>Clause removed</p>
--	---	---

	<p>If this is expected to ensure that past history of exposure will be kept then it is doomed to failure. Most people can't even keep/find previous films in many cases as it is now. They would have even less chance of retaining paper records or remembering if or when they have undergone radiological procedures.</p> <p><b>2.2.1: line 193</b> The word 'objects' be replaced with 'objectives' for clarity.</p> <p><b>2.2.1: line 196 -197</b> For regulatory convenience this should be a separate sub-clause.</p> <p><b>2.2.2: line 199</b> 'including the case of irradiation of a child' should be removed as children are never in a position to give informed consent and hence this is covered by the preceding statement (line 198).</p> <p><b>2.2.3 line 202-5</b> Just not practicable to expect subjects to keep such records (see previous comments).</p> <p><b>2.2.4 line 206-207</b> This is not really a responsibility of the human subject or guardian. This is a 'right' of a human subject or guardian and hence should not be included under the heading of the 'Responsibilities of the Subjects or Guardians of Subjects'. This issue has been adequately covered in Section 2.1.6.</p> <p><b>2.3 line 221-223</b> We recommend that the HREC should require a medical physicist or equivalent to sign-off on any relevant project as a requirement? Not just that "Particular attention should be given to:" – line 216. Again we would suggest this advice be placed in a Safety Guide.</p> <p><b>2.3.2(c) &amp; (d): lines 221 - 227</b> (Also see comment 2.1.9) Once again this seems to be placing much more onus on the Regulator than is currently the case in Victoria, at least, since normally research protocols are only submitted for regulatory review after they have received approval of the HREC.</p>	<p>Working group appreciates the obstacles involved however potential benefits in retaining the clause in terms of subject awareness was considered worthwhile</p> <p>Clause 2.2 removed as it is covered by clause 2.1 or the NHMRC National Statement</p> <p>Clause 2.2 removed as it is covered by clause 2.1 or the NHMRC National Statement</p> <p>Clause 2.2 removed as it is covered by clause 2.1 or the NHMRC National Statement</p> <p>Clause 2.2 removed as it is covered by clause 2.1 or the NHMRC National Statement</p> <p>Clause 2.2 removed as it is covered by clause 2.1 or the NHMRC National Statement</p> <p>Accepted</p> <p>Accepted. The regulatory authority's role in verification of the information provided to the HREC has been replaced with responsibilities for the radiation medical physicist</p>
--	---	--

	<p><b>2.3.2(f): line 230</b> Insert the word ‘radiation’ before the word ‘doses’.</p> <p><b>2.3.3: line 232 - 239</b> The sub-clause (lines 236-239) ‘Human Research Ethics Committees must <del>therefore</del> ensure that they have access to appropriate radiation advice sufficient to permit a full understanding of the radiation aspects of the proposed research prior to recommending that such research proceeds.’ seems to be the main part of the clause. Lines 232 to 236, that is, ‘A recommendation from, or an approval issued by, a Human Research Ethics Committee indicating that the proposed research meets ethical requirements carries the implication that the Human Research Ethics Committee has considered the radiation related risks of the proposed research.’ is mere commentary that would be more appropriate to appear in a Safety Guide and not in the Code. At a minimum, the clause should be turned around and lines 236-239 should precede lines 232 to 236.</p> <p><b>2.4; Lines 241 to 244</b> Some responsibility with the overall observance of this Code should lie with either the principle researcher and/or the Organisation conducting the research. The definition of the responsible person does not capture either the principle researcher and/or the Organisation. Using the definition in the Code either the Company/Radiation Safety Officer owning and/or having control of the equipment is responsible and not the research company/person instituting the research. The research company/person can sometimes be a third party entity to the place where the exposure to ionizing radiation takes place. It would make sense to capture research company/person in addition to the facility at which the exposure to ionizing radiation is taking place as being responsible for the overall observance of this Code.</p> <p><b>Page 9</b> <b>3. Lines 254 - 262</b> This statement is a little bit ambiguous and tends to imply that approval from the regulatory authority is required prior to the HREC giving approval. Vis-à-Vis 2.1.9 lines 162-165, and, 2.3.2 (d) lines 224 – 227. Also refer to 2.3.3 in which it states that the HREC has assessed and considered the radiation related risks of the research. The implication is that this done prior to it being submitted to the relevant regulatory authority.</p> <p><b>Table 1.</b></p>	<p>Clause has been removed as the requirement is covered by the NHMRC National Statement</p> <p>This clause has been removed as the code has been restructured to specify responsibilities for the radiation medical physicist that will ensure appropriate radiation advice is provided to the HREC</p> <p>Responsible person removed.</p> <p>Has been changed to refer to medical physicist</p> <p>Involvement of regulatory authority has been removed from the HREC process</p>
--	---	---

The effective dose to children under 2 years has been set at a figure of 0.1 mSv. This is the dose obtained in about 3 weeks of natural background in Australia. Additional doses of several mSv per annum can be obtained by moving house. It seems to be hard to justify referring such ludicrously small doses to the regulatory authority. Is there any evidence that would make 0-2 years more affected by minor doses than other children? This distinction should be removed and the dose constraint should be set at 0.5 mSv for all children. This is still 10 times less than the value for adults and gives a substantial degree of protection for all children.

Apart from the additional pointless work generated for regulatory authorities, a limit of 0.1 mSv implies that there may be some concern about doses of this order. If this is the case it will create problems in all sorts of areas. For example, general radiation protection of the public (which includes children) has a dose constraint of 1 mSv. If 0.1 mSv should be used there may be problems in planning radiation protection where young children may be present.

The dose constraint for the equivalent dose in adults should be tied to other limits that are well defined (e.g. dose limits for occupational workers) for reasons noted below. Reference to ICRP 85 is only appropriate in the context of skin and eye damage. Also, the present statement (a portion of any organ) is ill defined. How small should a portion of an organ be? Is it really necessary to have equivalent dose constraints for organs other than the eye, hands & feet & skin? Surely, other organs are protected from deterministic effects by the dose constraints on effective dose.

We cannot see how the 200 mSv cumulative equivalent dose constraint for children will work given that, of necessity, it will require an individual and/or multiple organisations to keep and/or share records for up to 18 years.

***Page 10***

***Annex I, line 280***

The risk referred to here is for stochastic risk, which may not be the only possible risk. Modify accordingly: "The level of risk for stochastic effects can..."

***Annex I, line 289***

The ICRP stance is hardly "recently" any longer. Omit this word.

***Pages 12 and 14***

Changed values. 0.1 mSv only applicable to exposure of fetus

	<p><b>Annex 2 &amp; 3</b> To all intentional purposes the dose limits are presented twice. Surely they should be in one table. Suggest removal of Table in Annex 3 and all references to it.</p> <p><b>Page 13</b> <b>Annex 3: lines 402 &amp; 409</b> Suggest that the number 100 mSv be altered downwards to 50 mSv in lieu of latest LSS findings [see Pierce et al; Radiat Res 154 (2000) 178-186; Health Phys 85 (2003) 43-46], which are consistent with a risk down to at least 50 mSv. Thus, line 402 should be changed to: “Data indicates that doses above approximately 50 mSv, received in a short period, may lead ....” Line 404 should delete the word “good” as the epidemiological evidence is not that convincing.</p> <p><b>Page 22</b> <b>Glossary: lines 678-689</b> The definition of a Medical Physicist needs to be slightly reworded. Lines 679-680 define the requirements. The subsequent lines indicate how individuals may meet those requirements. Accordingly, we suggest having a period after monitoring in line 680 and then starting a new sentence with “A suitable person should: ”.</p> <p><b>Lines 690-693</b> The inclusion of the defined unit mSv creates problems as such. If it is retained then Sv and Gy (mGy?) need to be defined as they are used in the COP. However, the real issue is that the mSv as defined relates to dose equivalent when it is equally valid as the unit of effective dose. This is not easy to resolve. We suggest leaving out all glossary terms relating to radiation units and just refer to them as footnotes (as is done already on page 13 &amp; 16)</p>	<p>Definition has been re-worded to be consistent with other Codes</p>
<p><b>018</b> Simon Critchley QLD Health</p>	<p><b>Line 28</b> should be “...include but are not...”</p> <p><b>Line 53</b> should be “...research is given...”.</p> <p><b>Lines 92 and 93.</b> I suspect that, instead of referring to the Australian and New Zealand Society of Nuclear Medicine here, we should instead be referring to the Australian and New Zealand Association of Physicians in Nuclear Medicine (ANZAPNM) as this would be the more appropriate body.</p>	<p>Accepted</p> <p>Accepted</p> <p>Accepted</p>

	<p><b>Line 99</b> should be "...details of the information...".</p> <p><b>Line 122.</b> Instead of referring to "problems", perhaps we should use another less emotive word such as "matters" or "conditions".</p> <p><b>Line 124</b> should be "...involving the irradiation...".</p> <p><b>Line 129.</b> Should "selection" be used instead of "choice".</p> <p><b>Line 144</b> should be "...research, and...".</p> <p><b>Line 152.</b> All history is "past". Therefore the use of the word past is redundant. Should be "...whose radiation history...".</p> <p><b>Line 199</b> should be "...case of the irradiation...".</p> <p><b>Lines 256 to 259</b> should be amended to "...unless the Human Research Ethics Committee is provided with specific advice from the relevant regulatory authority or a medical physicist in relation to any proposal to exceed these dose constraints."</p> <p><b>Lines 272 to 273</b> should be changed to "Any proposal to exceed these values must be referred for advice to the regulatory authority or a medical physicist."</p>	<p>Accepted. Clause expanded</p> <p>Accepted</p> <p>Accepted</p> <p>Accepted</p> <p>Accepted</p> <p>Clause deleted</p> <p>Clause deleted</p> <p>The regulatory authority has been replaced with a radiation medical physicist</p> <p>Regulatory authority referral has been removed and replaced with verification by a second medical radiation physicist</p>
<p><b>019</b> Susan O'Connor University of Newcastle</p>	<p>Thank you for the invitation to comment on the above Draft Code. ARPANSA is to be congratulated on its initiative to develop the Code and the assistance it will provide to Human Research Ethics Committees.</p> <p>Very briefly, I would just like to comment on one point. In relation to <b>2.1.1(d)</b> and <b>2.1.12(d)</b> of the Code, the information to be provided to the Human Research Ethics Committee and to the research participants should include a lay person's description of the radiation exposure which uses benchmarks that would be meaningful to members of the public. Stating the dose as x millisieverts does not provide potential participants with the information they require in order to make an informed decision about the relative risks.</p>	<p>Accepted. Model risk statements incorporating these elements have been included in annexes</p>
<p><b>020</b> Zachary Alach</p>	<p><i>Mary Aerts</i> <i>Physicist - Radiation Health Branch</i></p>	

<p>Radiation Health Branch Department of Health, WA</p>	<p><b>CODE OF PRACTICE</b> <b>Foreword:</b></p> <p>Could the second sentence of para 5 be reworded to something such as “The Code of Practice applies to research for medical information and investigative clinical trials . . . “</p> <p>The phrase in the second sentence “therapeutic trials” could cause confusion about what the Code encompasses even though this is elaborated under 1.4 Scope. The word “therapeutic” can be ambiguous (no doubt it was meant in its broadest context, but it could be interpreted as meaning ”radiotherapy”). Also, as worded, the first part of the second sentence could imply that <i>only</i> “therapeutic clinical trials“ are covered.</p> <p><b>Recruiting of volunteer subjects</b></p> <p>In the past, it has generally been regarded as unsuitable to recruit students associated with the researcher or to recruit patients with diseases unrelated to the proposed study, because of the sensitivity of the student/supervisor and patient/doctor relationships. I believe this was stated in one NHMRC document at least in regard to students associated with the researcher.</p> <p>I cannot find mention of this point in the Code – did the Working Party have a reason for omitting it? Was it felt that this was covered in other ethics documents? , and even if so, would it be appropriate to reference that here?</p> <p><b>2.1.3 (a)(ii) (line 111):</b></p> <p>Child should be defined (presumably the legal &lt; 18 years)?</p> <p><b>Section 3: Table 1 footnote e (lines 275 &amp; 276):</b></p> <p>The lens mention in footnote e needs to be re-worded.</p> <p>200 mSv is a factor of 10 below the 2 Gy threshold for transient erythema (ICRP 85, Table 3.1). The lens is also relevant and should be referred to, but 200 mSv is <b>not</b> necessarily a factor of 10 below the threshold for detectable lens opacity (it’s a factor of 2.5 – 10 below for single exposure, and potentially</p>	<p>Noted</p> <p>This is not radiation specific advice and is covered by the National Statement</p> <p>Age limit as defined in Table 1 is for children up to the age of 18</p> <p>Agreed</p> <p>Accepted</p>
---	--	---

	<p>more than the threshold for protracted if unlikely long-term exposure).</p> <p>ICRP 60 gives thresholds for detectable lens opacities as 0.5 - 2 Sv from single brief exposure (cf ICRP 85's 1-2 Gy from fluoroscopy), 5 Sv from total highly fractionated or protracted exposure, and &gt; 100 mSv/yr for highly fractionated or protracted exposure for many years. Should there be a further dose constraint on lens of eye of 100 mSv in any year? (even though it is unlikely that a volunteer subject receiving 200 mSv to the lens annually would do so for 25 years thus making the 5 Sv threshold total.)</p> <p><b>Glossary: definition of medical physicist (lines 685 - 689)</b></p> <p>Suggestion: to (b) lines 685 - 689, add "(as relevant to the requirements of this Code)", ie:</p> <p>"(b) has an equivalent level of training and skills, knowledge and expertise (as relevant to the requirements of this Code) to a person accredited in Radiological Physics or Nuclear Medicine Physics by the ACPSEM as determined by the relevant regulatory authority, and specifically approved by the relevant regulatory authority to make estimates of radiation doses in research projects."</p> <p>Given the current shortage of medical physicists, the practical reality is that it may be necessary to use medical physicists who have expertise in relation to the requirements of the Code but do not have ACPSEM accreditations or comprehensive equivalent.</p> <p>The relevant regulatory authority would not need to assess the person for <i>complete</i> equivalence to the accreditation (which the person might not have or might not need, and the relevant regulatory authority probably wouldn't want to take on such an assessment anyway) – the relevant regulatory authority simply needs to assess them for equivalence <i>in relation to the requirements of the Code</i> ie to perform the necessary dosimetric calculations, measurements and monitoring.</p> <p><b>RIS</b> <b>Item 3:</b> Confusion with the use of the word "source", and x-rays have been omitted.</p>	<p>The existing definition includes 'for the purpose of this code'</p> <p>Opening statement has already acknowledged the scope of the definition</p> <p>Agreed this is also acknowledged in the existing definition where the regulatory authority is given discretion in defining who can undertake the responsibilities of the radiation medical physicist</p> <p>Agreed the existing definition specifies that the regulatory authority's determination is with regard to the estimating of radiation doses in research projects</p>
--	--	---

**Item 4:**

As quoted here, it is implied that reporting to the regulatory authority was mandatory for those with effective doses less than 5 mSv.

In WA, *all* research projects using ionising radiation must be approved by the Human Ethics Committee of the institution.

However WA regulatory authority approval is mandatory *only* where the effective dose (beyond that received from normal medical management) exceeds:

- 5 mSv in any year and an average of 1mSv per year over 5 years for adults
- 0.5 mSv in any year for children or those incapable of giving informed consent
- 0.1 mSv in any year for infants, babies or foetuses.

Below these levels, the assessment may be carried out by the institution's Radiation Safety Officer and/or Radiation Safety Committee. The Radiation Safety Officer may elect to provide the regulatory authority with information.

**Item 32 (e)**

Correction (italicised words should be added):

First "required where" point: the effective dose *to an adult* exceeds 5 mSv

Last "required where" point: the radiation dose to any individual in any 5 year period exceeds an average effective dose of 1 mSv per year.

*Radiological Council  
Western Australia*

**CODE OF PRACTICE:**

**Section 3: Table 1**

In Section 3 Table 1, the draft CoP has retained the 0.1 mSv as the dose constraint for children from conception to 2 years. Above this value the research has to be referred to the regulatory authority.

Changes to be incorporated in revised draft

Correction noted

	<p>Although Western Australia had previously adopted the NH&amp;MRC No. 12 as a registration condition for hospitals undertaking research using ionising radiation, there is some concern at the low level required to be reported for exposures for those aged 0-2 years. Considering 0.1 mSv is the dose obtained in about 3 weeks of natural background in Australia, and additional doses of several mSv per annum can be obtained by moving house, it seems difficult justifying referring such small doses to the regulatory authority. Also there is no acknowledged evidence that would make 0-2 years more affected by minor doses than other children. It is recommended that this distinction be removed and to set the dose constraint at 0.5 mSv for all children. This is still 10 times less than the value for adults and gives a substantial degree of protection for all children.</p> <p>Apart from the additional work generated for regulatory authorities, this limit implies that there may be some concern about doses of this order. If this is the case we open an enormous number of problems in all sorts of areas where, protection of the public (which includes children) has a dose limit of 1 mSv. It is suggested that perhaps if 0.1 mSv is used, it may have ongoing implications for radiation protection planning.</p> <p>It has been strongly argued from within the Radiological Council of Western Australia that this limit should be changed.</p>	<p>Agreed. Table 1 amended</p> <p>Agreed</p> <p>Responsibility for verification of dose estimates has now been assigned to medical physicists</p>
<p><b>021</b> Dr Kerry J Breen Chair Australian Ethics Committee NHMRC</p>	<p>The provision of accurate and appropriate advice to researchers and Human Research Ethics Committees (HRECs) regarding the use of ionising radiation in research involving humans is strongly supported. As you are aware the NHMRC and AHEC have responsibility for providing guidance to researchers and HRECs on the ethical conduct of research involving humans. It is important that advice on the use of ionising radiation for research purposes, issued by the Australian Radiation Protection and Nuclear Safety Agency (ARPANSA), is consistent with the principles and advice provided in the NHMRC <i>National Statement on Ethical Conduct in Research Involving Humans</i>. For this reason it is proposed that AHEC and the Radiation Health Committee liaise closely on the development of this Code.</p> <p><b><u>Draft Code of Practice: Exposure of Human Subjects to Ionising Radiation for Medical Research Purposes</u></b></p> <p>Background</p>	<p>Accepted. The purpose has been amended to clarify that the code provides radiation specific advice and that the NHMRC National Statement provides other advice relevant to research with humans</p>

The Australian Health Ethics Committee (AHEC) is a principal committee of the National Health and Medical Research Council (NHMRC). The NHMRC is established under the National Health and Medical Research Council Act (1992).

The Act establishes that the functions of AHEC are:

- a. to advise the Council on ethical issues relating to health; and
- b. to develop and give the Council guidelines for the conduct of medical research involving humans; and
- c. such other functions as the Minister from time to time determines.

The Council, being cognisant of the requirements of the Act, has formulated the following terms of reference, which incorporate additional functions for AHEC:

1. To develop and give the Council guidelines for ethical conduct in the health field, in addition to those required for function (b) above, and for the purposes of the *Privacy Act 1988*.
2. To conduct and promote education and training in research ethics for members of Human Research Ethics Committees and the research community.
3. To advise, support and facilitate the work of Human Research Ethics Committees.
4. To develop, advise the Council on, and apply mechanisms to monitor the use of and compliance with guidelines issued under functions (b) and (1) above.
5. To promote community debate, and consult with individuals, communities and governments on ethical issues relating to health.
6. To keep abreast of international developments in relation to health ethical issues and liaise with relevant international organisations and individuals

The *National Statement on Ethical Conduct in Research Involving Humans* (1999) (National Statement or NS) is the principal guideline developed by AHEC in accordance with function (b) above. It applies to all disciplines of research involving or impacting upon humans, whether health, medical, social or behavioural research. The National Statement is endorsed by the:

- Australian Vice-Chancellors' Committee;
- Australian Research Council;
- Australian Academy of the Humanities;
- Australian Academy of Science; and
- Academy of the Social Sciences in Australia,

and is supported by the:

- Academy of Technological Sciences and Engineering.

### **General Comments**

The provision of accurate and appropriate advice to researchers and Human Research Ethics Committees (HRECs) regarding the use of ionising radiation in research involving humans is strongly supported. It is important that advice on this matter, issued by the Australian Radiation Protection and Nuclear Safety Agency (ARPANSA), is consistent with the principles and advice provided in the National Statement. For this reason it is proposed that AHEC and the Radiation Health Committee liaise closely on the development of the Code.

The scope of the National Statement is 'research involving humans' whereas the scope of the draft Code is confined to medical research. Whilst it is appreciated that the majority of research involving ionising radiation will be in the medical setting, medical research is itself not defined in the Code. It is feasible that some research involving humans which also involves exposure to ionising radiation would not be captured within the Code. If so, it is not clear whether another code would apply, whether there would be a gap in the advice / standards applicable in this situation or whether the scope of the Code should be extended.

It would seem appropriate that a single code apply to all research involving humans where participants are exposed to ionising radiation. This would be consistent with the National Statement.

Also consistent with the National Statement would be the use of the term 'research participant' rather than 'human subject'. The latter term connotes an unequal relationship between researcher and research participant which is now seen to be inconsistent with the ethical principle of 'respect for persons'. The term 'research participant' has been used by the NHMRC since 1999.

Many of the principles and specific advice contained in the Code are well

Accepted. the term 'human subject' will be replaced with

	<p>aligned with the National Statement and, in fact, reiterate the content of the National Statement. Hence, some of this advice could be removed from the Code given that researchers and HRECs will be using the National Statement as the foundation document and the Code as additional advice for this specific research situation. It would seem sensible for the Code to only provide advice that is specific to this type of research as, in AHEC's opinion, the Code ought always be used in conjunction with the National Statement, whether by a researcher or an HREC.</p> <p>Given that the Code will be used by researchers and HRECs who will have varying familiarity with research involving ionising radiation it is recommended that the Code serves to orientate the reader. Firstly, a brief history of the previous codes/guidelines and the status of the current Code could be given. Secondly, a layperson's description of ionising radiation including examples of the common sources and uses of radiation would be useful. Information about the risks of radiation, how risks can be minimised and how risks might be balanced by benefits with reference to international standards should be next. An overview of the regulatory framework for radiation use and the role of state regulatory agencies would be useful at this point followed by the role of the HREC in this framework. The Code could then outline the specific matters that need to be considered by researchers, in conducting research, and HRECs, in reviewing and approving research, involving ionising radiation. These latter components would serve as the actual guidelines to be followed.</p> <p>It is suggested that information in the order given above would be more appropriate to this particular audience than the current order of information in the draft Code. The assessment of risk and benefits contained in Annex 1, for example, would seem important enough to warrant inclusion in the guidelines part of the document rather than an annexure. Weighing the balance of risks and benefits is an essential element of the work of HRECs and should be a consideration of researchers when designing research projects.</p> <p><b>Specific comments</b></p> <p><u>Scope (1.4)</u></p> <p>The description of the scope of the Code is somewhat confusing with regard to the type of medical treatment to which it applies. It is understood that radiation used in routine clinical care should not be the subject of special provisions such as those contained in this Code. However, using the expression '<i>does not</i></p>	<p>'research participant'</p> <p>Clauses that are not radiation specific or duplicate the advice in the National Statement have been removed</p> <p>This information is covered in the foreword</p> <p>Annex 1 and the annexes provide more general information and advice. Background material can be found in the regulatory impact statement</p> <p>Include general statement regarding the National Directory in the Foreword of the Code</p> <p>Accepted. Scope has been modified to emphasise the application of the code to radiation exposures that are in addition to those that are part of normal clinical management</p>
--	---	--

*apply where the patient receives a direct medical benefit from the administration of the ionising radiation...*' would unintentionally exclude all research where the use of radiation was known to be of benefit to patients but :

- the extent of that benefit was unknown; or
- the comparability of that benefit to other treatments was unknown; or
- the side effects of that use were not known and were being investigated.

It would also be confusing in situations where it is not known whether the administration of the radiation will be of benefit or not.

Hence the distinction that needs to be made is not whether the patient benefits from the radiation but whether the radiation is given as a component of routine care or as a component of research. The Code should only apply to research.

If the use of ionising radiation is a component of research it then needs to be clarified as to whether the radiation is itself the subject of research or the use of radiation is as a tool to aid the research. Radiation which is experimental would of course require careful consideration by the HREC.

Radiation as a tool would not need special attention if used as part of clinical practice AND is not additional to the exposure that the person would have received during normal care. HRECs will however consider carefully any exposure to radiation which occurs as a direct result of the person's participation in the research even if the nature of that exposure is the same as that used in normal care. The issue being that the participant would not have been exposed to that radiation, and the associated risk, if not for their participation in research.

#### Researcher (2.1)

Much of the detail described in this section repeats the basic requirements of the National Statement and therefore does not need to be repeated. The inclusion of such detail may be misinterpreted by researchers and HRECs to imply that a higher or different standard is being applied.

#### Age and Pregnancy (2.1.3)

The intent of these paragraphs would seem to be that the risks of the research must be minimised and be balanced against the potential benefits of the research. This is entirely consistent with the principles of the National Statement. However, the prescriptive nature of the paragraphs is unnecessary, could be interpreted as paternalistic, in that it precludes the exercise of autonomous and informed choices, and may in fact hinder appropriate research.

National statement is not a regulatory document that can be used by radiation regulators. However, non-radiation aspects of the draft Code have been removed.

Not accepted. Radiation has specific and well established risks in pregnancy. Clauses are consistent with international best practice.

	<p>2.1.3 (a) (iii) regarding foetuses is confusing given the following paragraphs relating to pregnancy. Is it intended that this paragraph apply to in vitro embryos? If so, this section could perhaps be written with reference to the NHMRC <i>Guidelines on Assisted Reproductive Technology</i> where guidance is given on the limitations on the use of embryos in research.</p> <p>2.1.2 regarding verification of radiation specific information – it should be explained whether this requirement is a regulatory one and whether it can be satisfied in ways other than those listed as some institutions or HRECs may have other mechanisms in place.</p> <p><u>2.2 Subjects or guardians of subjects</u></p> <p>It is recommended that advice regarding obtaining consent from parents/guardians of children be addressed separately to that of legal guardians and next of kin for adults. It is otherwise confusing. In addition, it is recommended that unless there is a need to provide advice on this subject which is specific to research involving ionising radiation the section should be kept brief and refer to the relevant guidelines in the National Statement</p> <p>2.2.1 – the use of the word ‘objects’ is somewhat legalistic. In addition, it is not possible to ensure that a person has understood the risks of the research. It is sufficient to request that the risks have been explained to the person in way that is appropriate to their level of comprehension and that the person has had the opportunity to ask questions. Again, reference to the National Statement would assist.</p> <p><u>Human Research Ethics Committee (2.3)</u></p> <p>No definition of an HREC is given. It would seem appropriate to indicate that the HREC should be one operating in compliance with the National Statement and registered with the NHMRC.</p> <p><u>Person responsible (2.4)</u></p> <p>‘Responsible person’ is a legal term in many jurisdictions referring to the person who is legally able to make decisions for another person, particularly with regard to medical treatment. Hence, it may not be appropriate to use that term for any other purpose in a document that will be read by an audience that will be familiar with its legal meaning in other contexts. It would be appropriate to use another term. If however, this term is used in radiation related legislation it will be necessary to somehow clearly distinguish between the two concepts.</p>	<p>Clause deleted.</p> <p>Requirement is to prepare submission. Duplicate statements removed, only statements relevant to radiation retained.</p> <p>Section removed as it is covered by clause 2.1 or NHMRC National Statement</p> <p>Definition to be added to glossary</p> <p>Definition is included in the glossary. Appreciate the difference; however do not foresee this difference having any impact in this context. Responsible person clause removed</p>
--	---	---

<p><b>022</b> <b>Len Potapof</b> <b>NSW EPA</b></p>	<p><b>Comments on the RIS</b></p> <p>The RIS contains good explanatory material but is incomplete in quantification of costs and benefits. It may be the case that ARPANSA simply was not able to provide estimates of costs and benefits. However, despite calling for (unknown) cost information (paragraphs 78 &amp; 83) ARPANSA have concluded that Option 3 will return a net benefit (paragraph 90).</p> <p>Paragraph 77 sets out benefits, however these are not all benefits. Some are statements of the differences between the Code and RHS 12 and others are new requirements that have both benefits and costs. For example:</p> <ul style="list-style-type: none"> <li>• “Total cumulative effective dose of 5 mSv for children to age of 18 years” is stated as a benefit because in RHS 12 there was no equivalent, although at paragraph 40 suggest RHS 12 effectively did set a limit of 8.3 mSv. e.g. we could set a cumulative effective dose in the Code of <b>20</b> mSv, and this would still be claimed as a benefit because there is “no equivalent provision” in RHS 12; or we could set a cumulative effective dose under the Code of <b>zero</b> mSv, and this would presumably be a benefit because it caps the radiation level, even though it would end all child-related medical research that required use of ionising radiation.</li> <li>• Similarly, statements of “inclusion of responsibilities” are not benefits in themselves, they are new requirements that have both benefits and costs. The inclusion of responsibilities for groups other than the HREC is likely to lead to some other benefit eg simpler record-keeping and administration, lowered risks of overexposure for research subjects in vulnerable sub-groups etc.</li> <li>• ‘Researchers must estimate the absorbed skin dose for multiple CT scans or prolonged fluoroscopic screening’ - this entails a cost to the researcher, but could create a significant benefit by avoiding over exposures - again, this statement in the Table is not a benefit but a procedure, and could have been evaluated.</li> </ul> <p>The RIS provides figures in identifying exposure numbers and risk levels, however it would have been more useful if it actually identified the costs to organisations of adopting the proposed Code e.g. providing a cost at paragraph 85 for researchers to provide information to their HREC. It is not clear as to what the costs of implementation will be.</p>	<p>Section on benefits of Option 3 has been replaced with cost-benefit analysis undertaken by Allen Consulting</p>
---	--	--

	<p>As with previous RISs, prepared by the Commonwealth, the lack of quantitative analysis means that this RIS does not satisfy the subordinate legislation requirements of NSW and should be re-done.</p> <p><b>Comments on the Code</b></p> <p><b>General</b> The role of the Authority is to oversee and approve the use of radiation within its jurisdiction, and provide advice to organisations regarding legislative requirements for the use of ionising radiation, particularly in terms of radiation safety. The DEC does not agree with the proposal of making the ethics committee the approving body for research proposals involving the use of radiation.</p> <p>The DEC recommends that the status quo be maintained, explicitly that the Authority remains the ‘independent’ approving authority for medical research proposals involving the use of radiation.</p> <p>If it is decided that the ethics committee into remain the sole determining authority for such research then the code should be amended to allow the ethics committee to determine the most appropriate mechanism for assessing these applications.</p> <p><b>Section 2.1.2f (i)</b> It would be better if the relevant facility in question adheres to the ANZAPNM accreditation programme rather than the ANZSNM QA programme. The latter details technical specifications of gamma cameras, but the former relates also to clinical conduct and radiopharmaceutical QA (as well as machine specifications) and is thus more suitable.</p> <p><b>Section 2.1.3 (a) (iii)</b> That the terms ‘appropriate health or medical authority’ be clarified.</p> <p><b>Section 2.1.3 (b)</b> If there is a need to conduct research during pregnancy, there is no advice on recommended exposure limits to pregnant women and the foetus and/or approval by the ethics committee or authority.</p> <p><b>Section 2.1.3 (iv)</b> It may be useful if the footnote ‘Pre-menopausal potentially fertile women should have a serum pregnancy test to exclude pregnancy before</p>	<p>Regulators will continue to determine use of ionizing radiation for research purposes through licencing and registration mechanisms. The Code aims to ensure that HREC’s and research participants are provided sufficient and accurate information to make informed decisions regarding proposals and participation</p> <p>Code is now focussed on providing accurate radiation information to HREC and participant for their decision to proceed</p> <p>Accepted and changed.</p> <p>Clause deleted</p> <p>Clause clarified</p> <p>Clause modified</p>
--	---	---

	<p>commencement of the radiological investigation’ be made a requirement of the code. In addition a urine sample is considered to be as accurate as a serum pregnancy test. Perhaps a urine sample being the more preferred/comfortable procedure should be used/indicated.</p> <p><b>Section 2.1.9</b> the wording in this paragraph be removed and replaced with wording to reflect the recommendations made by DEC above under general comments e.g. the researcher must seek approval of the authority when the research proposal is undertaken on research subjects (excluding terminally ill subjects), who do not receive a direct benefit from the proposal and where the radiation dose exceeds 5 millisievert of the cumulative dose equivalent to any individual subject in any year (as indicated in Table 1).</p> <p><b>Section 2.1.12</b> states that a ‘researcher must ensure that the ethics committee is provided with specific advice either from the regulatory authority or a medical physicist’, this appears to be in contradiction to section 2.1.9 where it recommends that advice be sought only from the regulatory body.</p> <p>It also recommended that the wording ‘verification or..... medical physicist,’ be deleted as it is up to the determining authority within each jurisdiction to establish a mechanism for assessing these applications.</p> <p>Please refer to comments Section 2.5 for further comments in relation to the role of the regulatory authority.</p> <p><b>Section 2.5</b> It is recommended that this section be removed or that the wording of this section be amended as a code cannot impose a role onto a regulatory authority. Please refer to comments in Section 2.1.9.</p> <p><b>Annex 1</b> The terminology used, in Annex 1 of the draft ARPANSA code, to represent the “Level of Risk” does not follow the nomenclature that has more recently been used to communicate risk. It is considered that the values used in Annex 1 exaggerate the risk and that it would be unsuitable to be used in a Patient Information Statement and Consent Form as the patient would be likely to believe that the risk is higher than the actual risk from the radiation exposure. It is recommended that Annex 1 including the table not be used in its current form.</p> <p>It is recommended that ARPANSA consider replacing Annex 1 of the draft</p>	<p>Replaced with biochemical test</p> <p>Independent verification by second radiation medical physicist should eliminate conflict of interest issues</p> <p>Clause removed</p> <p>Clause changed to ensure independent verification</p> <p>Agreed.</p> <p>Agreed. Annex 1 amended</p> <p>Standard patient information statements have been added to annex 2</p>
--	---	---

Code with the preferred terminology adopted by NSW Hospital and University Radiation Safety Officers Group (HURSOG) Guideline *Research Protocols Using Ionizing Radiation in Human Volunteer* as provided in the table below.

Agreed. Annex amended

Terminology	Risk estimate	Effective Dose range
negligible	<1:1,000,000	< 20 uSv
minimal	<11,000,000 and 1:1,000,000	20 uSv to 200 uSv
very low	between 1:10,000 and 1:100,000	200 µSv to 2 mSv
low	between 1:1,000 and 1:10,000	2 mSv to 20 mSv
moderate	between 1:100 and 1:1,000	20 mSv to 200 mSv

**Table from HURSOG Guideline: *Research Protocols Using Ionizing Radiation in Human Volunteers***

This terminology was developed by Professor Calman (UK Chief Medical Officer) and published in BMJ 1996, 313:799-802 and it uses the scale provided in the above table (under the heading risk estimate).

The HURSOG Guideline uses this terminology, together with ICRP risk coefficient of  $5 \times 10^{-2}$  / Sv for the probability of fatal cancer in the general population, based on ICRP Publication 60 (Table B-7), as provided in the table above (under the heading of effective dose range).

An effective dose of 2-5 mSv, as found in many common radiological studies (eg lumbar spine x-ray, bone scan, head CT) would be classified as having an “intermediate level of risk” by Annex 1, but as having a “low level of risk” using the Calman terminology. It is believed that an “intermediate level of risk” is inappropriate for studies that have a calculated risk of fatal cancer in the range 1:4000 - 1:10,000.

The table could be simplified further as follows:

Terminology	Risk estimate	Effective Dose range
minimal	< 1:1,000,000	> 200 uSv

very low	between 1:10,000 and 1:100,000	200 µSv to 2 mSv
low	between 1:1,000 and 1:10,000	2 mSv to 20 mSv
moderate	between 1:100 and 1:1,000	20 mSv to 200 mSv

Should Annex 1 be removed then the 2<sup>nd</sup> paragraph of Annex 1 (lines - part 297, 298 and 299) should be placed in the main body of the document along with further explanation of terminally ill patients.

The draft code contains an assessment of the risks versus benefits involved in the research protocol. This Annex contains proposals for exposure during pregnancy. These are based on the new ICRP recommendations (although the footnote referring to this document is missing from the draft Code) and require that the exposure should be kept below 1 mSv during the course of the pregnancy (9 months). This is equated to ‘the same level of protection as the general public’, which is 1 mSv over a period of 12 months and has been generalised from ‘medical workers’ to all occupational exposures.

**Annex 3** There may be too much credence given to the linear no threshold hypothesis. There is no evidence that this applies to low dose exposures, thus a more balanced argument should be provided and at the very least a discussion of radiation homeosis be included.

Noted

**023**  
**Ashford Cancer Centre**

We have identified what we see as an inconsistency in the draft which makes it somewhat problematic when it comes to the issue of clinical research in patients, particularly in our field of expertise, Medical Oncology.

On page 1 of the introductory section of the draft (1.4: Scope) the wording in the first paragraph seems to contradict the second paragraph as follows: “the code of practice *applies to* the exposure of human research subjects who *do not receive a direct medical benefit ....It also applies to radiological diagnostic studies used to monitor the outcome of therapeutic clinical trials*”. The second paragraph states that the code ..... “*does not apply* where the patient receives a *direct medical benefit* from the administration of ionising radiation *or where procedures are performed as part of the normal clinical management*”

(our italics).”

This contradiction has implications on the interpretation of the code when applied to the area of clinical trials in oncology, and in particular, the meaning of “a direct medical benefit” needs to be clarified. In oncology clinical research, the *direct medical benefit* could be that the imaging allows a true assessment of the patient's response to treatment to be made. Additionally, when the second part of the sentence is considered, ie *they would be performed as part of normal clinical management*, then the code will not be applicable to clinical research in the oncology setting.

It is agreed that exposure to ionising radiation has some adverse events, particularly when the radiation doses are excessive such as those given in the context of some nuclear medicine studies and very frequent diagnostic investigations such as CT scans. However, in the context of clinical trials in subjects with illnesses such as malignancies, the majority of radiological investigations are performed in line with standard clinical practice. That is, the frequency of CT scans, bone scans, x-rays and so on is generally not that dissimilar to that which would have occurred if the patient was not in the clinical trial. There are of course exceptions to the general rule but in our experience of over twenty years of participating in clinical trials it is extremely rare for any of these radiological investigations to be performed more frequently than every six to eight weeks, with the usual period between assessments being every eight to twelve weeks, ie the same frequency which we generally use to assess response of patients receiving standard chemotherapy or radiation therapy.

The radiation exposure received by these patient is more than that experienced by the general population, but as the patient population targeted by the majority of oncology trials usually have late stage disease and are not expected to survive beyond 24 months, the increased risk of developing cancer in the future from radiation exposure in most cases is irrelevant. In trials for patients with earlier stage disease, it is rare for patients to have any more scans than those required in standard

Application of the Code has been modified to apply to any radiation exposures in addition to those that are part of normal clinical management

Agreed and detailed in Annex 1

	<p>clinical practice, so again, even though the risk is greater than that in the general public, it is not greater than that of patients with early stage disease who are receiving standard chemotherapy or radiation therapy treatment off study. If these informed consent requirements are to be mandated for trial patients, then the logical extension is that as the risk is the same, the requirements should also apply to patients receiving standard therapy. This does not occur.</p> <p>We think it is therefore very important that ARPANSA incorporates into its final recommendation a general statement which unequivocally excludes the requirement for providing, in minute detail, information about the exact radiation dose that will be delivered to oncology patients enrolled in clinical trials. The only exception we would suggest to the proposed general statement would be situations where the frequency of radiological investigations are seen to be well outside and above standard clinical practice.</p> <p>We should note that statements about the frequency of radiological investigations are always mandated within the clinical trial informed consent documents, and patients are therefore fully informed if they are likely to experience an increased number of investigations, whether they be radiological or otherwise. This also applies to statements regarding general radiation risks, and we believe that excessive documentation of the total dose is probably academic, particularly for patients with malignancies who are unlikely to ever experience the long-term and hypothetical consequences of ionising radiation delivered from diagnostic sources.</p>	<p>Refer to amended scope</p> <p>Advisory material added to Annex 3</p> <p>Noted.</p>
--	---	---