



Response to Consultation on PTAC's Guidelines

Matters raised by the Breast Cancer Aotearoa Coalition (BCAC)

24 June 2008

PTAC's statutory role is to give objective advice to PHARMAC as to pharmaceuticals and their benefits (Section 50 of the New Zealand Public Health and Disability Act 2000 (NZPHD Act)).

PHARMAC's CEO states in his letter of 15 May 2008 that PHARMAC is "consulting broadly on changes to PTAC's Operational Guidelines to ensure optimal arrangements are in place for PTAC to provide free and frank advice to the PHARMAC Board".

With this goal in mind, and having examined the "Draft for Consultation" of the "Terms of Reference for PTAC and PTAC Subcommittees 2008", BCAC has a number of recommendations it wishes to submit to PHARMAC.

1. Criteria used by PTAC [Section 2.2.1]

In BCAC's view, one of the major obstacles to PTAC providing "free and frank advice" to the PHARMAC Board is the blending of financial criteria with clinical criteria that occurs at present. This has not been changed in the proposed new Terms of Reference.

According to the NZPHD Act, PTAC is an advisory committee established by PHARMAC to provide objective advice to PHARMAC on pharmaceuticals and their benefits. There is no mention of any need or requirement for PTAC to provide advice on the cost/utility of pharmaceuticals or their budgetary impacts.

Indeed there is no evidence that PTAC members have any particular expertise in considering the financial aspects of PHARMAC's brief. The current members of PTAC are "vocationally registered medical practitioners with expertise in clinical pharmacology, internal medicine and general practice" (Brougham letter, 15 May 2008). Similarly in the draft Terms of Reference it is stated that "in general, PTAC comprises senior health practitioners from multiple specialties selected for their expertise in critical appraisal as well as broad experience and knowledge of pharmaceuticals and their therapeutic indications" [Section 4.1.3] Clearly there is no requirement for PTAC members to have any expertise in the specialist area of conducting cost/utility analyses of pharmaceuticals to assist with public health funding decisions.

BCAC therefore contends that the following decision-making criteria should be removed from PTAC's Terms of Reference [Section 2.2.1]:

“(e) the cost-effectiveness of meeting health needs by funding pharmaceuticals rather than using other publicly funded health and disability support services;

(f) the budgetary impact (in terms of the pharmaceutical budget and the Government’s overall health budget) of any changes to the Pharmaceutical Schedule;

(g) the direct cost to health service users;

(h) the Government’s priorities for health funding, as set out in any objectives notified by the Crown to PHARMAC, or in PHARMAC’s Funding Agreement, or elsewhere”.

These are matters beyond a consideration of “pharmaceuticals and their benefits” as required of PTAC by the Act, and should not form part of PTAC’s criteria for assessing pharmaceuticals.

Clearly these matters will be considered separately by the Board of PHARMAC in any event, since they form part of the Board’s own criteria [Section 2.2.1]. There is therefore no need and no good reason for a committee established only for its medical expertise to address these points as well. Indeed, this could be interpreted as the PHARMAC Board not only delegating its functions to another body but one not qualified to make the assessment sought.

The Board of PHARMAC would be better served in its consideration of financial matters by obtaining advice from a separate committee of experts in pharmaco-economics, with the ability to give the Board high quality independent advice on the cost/utility of pharmaceuticals that have been assessed for their clinical benefit by PTAC. PTAC could have within its Terms of Reference a requirement that it provide its assessment of clinical benefits and risks in a format that will be useful to such experts, but PTAC should not make what will inevitably be amateur attempts to conduct such analyses itself.

BCAC understands that cost/utility analyses are performed mostly by PHARMAC staff at present. BCAC submits that a separate independent committee of experts in this field, operating in parallel with PTAC, would be a better mechanism for providing the PHARMAC Board with the independent, objective information it requires to apply its decision-making criteria.

BCAC asks that only criteria (a), (b), (c) and (d) be used by PTAC, and that the other criteria be omitted from its Terms of Reference.

2. Weighting factors [Sections 2.2.1, 9.3.2]

Also of concern to BCAC are the “weighting factors” PTAC can apply to the criteria. Section 2.2.1 states that PTAC is to give “such weight to each criterion as PTAC or its relevant subcommittee considers appropriate”. Section 9.3.2 notes that “PTAC will indicate which decision criteria it has given particular weight to in the course of making such recommendations”.

This generates considerable doubt about the quality of the PTAC’s entire decision-making process. As currently worded, the Terms of Reference [Section 2.2.1] ask PTAC to consider all the criteria

listed, but then give it the ability to downgrade or ignore any of these it likes, without any consistency from one application to the next, and without even having to provide reviewable reasons for doing so.

PTAC minutes, such as those of November 2007 on lapatinib ditosylate, indicate that at present PTAC discusses an application broadly, draws a conclusion as to its recommendation, and then lists the criteria relevant to the preceding discussion. BCAC suggests that a more transparent, objective and indeed more efficient process would be for PTAC to decide *a priori* the weighting that should be applied to each criterion, then to apply systematically each criterion to the case being discussed, to record the relevant discussion against each criterion in the minute, and to summarise with a reasoned argument for a final recommendation. BCAC suggests that such an approach would not only better demonstrate PTAC's objectivity and consistency in its approach to each application, but would in fact make PTAC's job easier than the less systematic approach taken at present. By taking this more structured approach, new PTAC members would more easily "come up to speed" with the decision-making process, perhaps resulting in a greater willingness for new members to join the committee when required.

3. Criterion (i) [Section 2.2.1]

BCAC contends that criterion (i), "such other criteria as PTAC sees fit", completely undermines the committee's entire process and should be omitted from the Terms of Reference. This criterion is too broad to be of any assistance to PTAC and actually provides it with the means to completely ignore any of the other stated criteria. Its inclusion in the Terms of Reference does nothing to improve the New Zealand public's confidence in the workings of PTAC.

4. Levels of evidence [Section 2.2.4]

"PTAC and its Subcommittees may rely on persuasive rather than conclusive evidence, if persuasive evidence is the best that can reasonably be obtained"

BCAC was concerned about this clause, which comes across as vague, unscientific and of dubious legal meaning. There are more formal definitions of the level of evidence that could be used in place of the terms "conclusive" and "persuasive". BCAC suggests that if such a clause has to be included at all, it should be replaced with the following:

"PTAC and its Subcommittees will review all available evidence in making their recommendations. The sources of the evidence and its level of strength will be noted in the minutes."

A suitable scale describing the level of strength of the evidence used should be either developed *de novo* or adapted from an existing source. By way of example we provide as Appendix 1 to the present document a scale showing the levels of evidence and used in the development of clinical best practice guidelines by the US National Comprehensive Cancer Network. This scheme has the additional advantage of allowing for the incorporation of differing degrees of consensus among

committee members into the final recommendation. BCAC recommends that PHARMAC and the Ministry of Health consider adapting this scheme if necessary, or developing something similar, and include it in PTAC's Terms of Reference.

Transparency and public confidence in process would be enhanced by a listing in the PTAC Minutes of the sources of evidence considered by the committee in making its recommendations.

5. Membership [Section 4]

Although BCAC notes that the process for appointment of PTAC members has been the subject of a previous consultation (see BCAC submission of 17th April 2008), there are some additional membership matters raised by the Terms of Reference.

In BCAC's discussion with the consultative group (19 June 2008, Auckland), the difficulty of recruiting PTAC members was noted by Dr Moodie and others. BCAC suggests that this task would be made easier if PTAC routinely sought advice not only from its sub-committees, but also from a wider pool of experts. This would not only bring new and relevant expertise to bear on each case considered by PTAC, but would expose more experts to PTAC's processes and would probably encourage more people to become involved, i.e. they would be familiar with PTAC's work, they would realise that the work of gathering data would be facilitated by direct approaches to people with relevant experience and expertise, and they would realise that a long-term commitment to serving on the committee would not necessarily be required.

BCAC notes that although there is a three-year term of appointment for members of PTAC (and its subcommittees), many members "roll over", so that currently PTAC has members who have served for 13, 11 (two members), 8 (two members), 5 (three members) and 4 years each.

BCAC suggests that there should be a finite term of appointment of three years and the appointees should be rotated off PTAC once they have reached this term to encourage new ideas, prevent entrenched views of a few members dominating the committee, and to draw in a wider pool of competent people with useful expertise. It will also encourage members to be more proactive about developing a "succession plan" and actively recruiting their replacements.

BCAC suggests that the Terms of Reference should include provision for PTAC to use not only the Subcommittee mechanism to acquire expert advice and data relevant to specific cases, but also to actively seek input from individuals and associations with relevant expertise on an *ad hoc* basis. The wide availability of electronic means of communication (email, skype, videoconferencing, etc.) should enable this approach, whereby a "project team" is assembled prior to the consideration of each application, rather than a standing committee relying entirely on its established, long-term membership to deal with information gathering and analysis in every case, then waiting until all members can arrange to physically meet in one place, followed by a slow process of minute checking and review. The seriousness of PHARMAC's business (people's lives and wellbeing are at

stake) means that the use of electronic media and any other means to speed up and improve the quality of decision-making, should be paramount.

BCAC also recommends that PTAC members ensure that their understanding of the mechanics of running clinical trials, especially the ethical aspects, is completely up to date. We note PTAC's minuted comments in relation to their consideration and rejection of proposals seeking funding for both trastuzumab and lapatinib that data was weakened and the magnitude of benefit will not be known because patients were switched to the treatment arm in studies. BCAC was concerned at a recent comment from a PHARMAC staff member (Jackie Evans), that "switching patients on to the treatment arm compromises the science of clinical trials" and "once patients enter a clinical trial they should stick with their assigned treatment" (PHARMAC meeting with BCAC 30 May 2008). Although Dr Moodie noted (at BCAC's 19 June 2008 consultation) that this was a matter of debate in the medical literature, BCAC notes that under the principle of beneficence the Belmont Report includes the general rules "do not harm" and "maximise possible benefits and minimise possible harms". We consider that moving patients on to the treatment arm as soon as benefits have been demonstrated conforms to these rules, whereas as preventing them from shifting would contravene them and might also bring into question not only the researchers' behaviour under the Belmont Report principle of "respect for persons" (Ethical Principles and Guidelines for the Protection of Human Subjects of Research, The National Commission for the Protection of Human Subjects of Biomedical and Behavioural Research, 44 Federal Register(18 April 1979), 23192-97), but also a potential breach of s 10 of the Bill of Rights Act 1990 especially if those participating in the trials are not made aware of the observed benefit of the treatment arm and not given the informed choice to switch to it. If adverse consequences to the participants in a trial flow from a decision not to permit them to switch to a treatment arm, those responsible for such a decision could expose themselves to criminal liability under sections 150A, 155 or 157 of the Crimes Act 1961. The use of a wider pool of expertise as suggested above, including legal and ethical advice should reduce this risk.

Some training in the ethical aspects of running clinical trials should be required for PTAC members to assist them with their understanding of trial design and the analysis of trial results, since this forms a crucial part of the evidence upon which PTAC makes its recommendations.

6. External communications [Sections 6.1.1 and 7.4.1]

BCAC is also concerned that some of the requirements in the area of external communications and public statements may compromise PTAC's ability (or, at the very least, the public's perception of it) to give "free and frank" advice to PHARMAC. Public perception is very important, the legal test being what an outside observer might reasonably perceive to be the case. Section 7.4.1 states that members may only speak to the media "... if they have the prior agreement of the PTAC Chair and PHARMAC staff". This condition effectively gags committee members from making statements to the media that are not first vetted by PHARMAC itself. Thus they become simply spokespersons for PHARMAC. This is not appropriate for a committee, which although a part of PHARMAC, is supposed

to exist in order to give objective advice to PHARMAC's Board. BCAC suggests that the 17th bullet point under Section 6.1.1, Responsibilities of the Chairpersons, be amended by deleting the phrase "having first obtained the consent of PHARMAC staff to the act of representation".

7. Responsibilities of all Members [Section 7.1.1]

BCAC suggests that the list of members' responsibilities should include an explicit requirement to review all relevant evidence and materials presented to them.

8. Conflicts of interest [Section 7.2]

This portion of the draft Terms of Reference refers only to the "guidance" set out in Appendix 4 (7.2.2) and makes no reference to ss 62-72 of the Crown Entities Act 2004 (CEA) which are set out in Appendix 3. BCAC suggests that members should familiarise themselves with the provisions of those sections of CEA and should be directed to them in section 7.2.1.

The conflicts to which 7.2.1 refers are non-specific and make no reference to 62(2) of CEA. The section refers to avoiding conflicts "to the greatest extent possible". BCAC suggests that clause is superfluous and meaningless. Members should avoid such conflict in accordance with the provisions of CEA.

7.2.2 makes no reference to the consequences of a conflict of interest as specified in s 66 of CEA or the consequence of failing to disclose it in s 67.

7.2.3 simply says that the Chair must consider the declared interest and "take any appropriate management or mitigation actions they deem necessary". BCAC suggests that this is not in accordance with CEA and that the Chair in fact has limited powers and not the broad discretion conferred by section 7.2.3. The law requires that a conflict of interest means that the member must not vote on the issue, must not take part in the discussion or any activity, must not sign any document and must be disregarded for the purpose of forming a quorum unless the chairperson is satisfied that it is in the public interest for the member to do so.

BCAC agrees that the fact of an acknowledged or perceived conflict of interest should be recorded in PTAC minutes as recommended in Appendix 4 and adds that if a Chairperson decides to invoke the "public interest" provision, this too should be recorded in the minutes.

9. Publication of Minutes [Section 9.4]

BCAC suggests that, in the interest of greater transparency, the names of all observers and attendees at PTAC meetings should be published in the PTAC minutes.

10. Appeal of decisions

While we understand that PTAC makes recommendations to the PHARMAC Board, which then makes decisions regarding recommendations to fund or decline to fund treatments, we believe there

should be a mechanism for appeal of recommendations and decisions that is less difficult, expensive, and daunting for patients than Judicial Review.



Elisabeth P.J. Burgess,

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APPENDIX 1: US National Comprehensive Cancer Network - Levels of evidence used in Guideline development

An extract from: [About the NCCN Clinical Practice Guidelines in Oncology™](#)

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http://www.nccn.org/professionals/physician_gls/about.asp

NCCN Categories of Evidence and Consensus:

When studying the recommendations on a pathway, the NCCN Guideline user should be given information about how the recommendation was derived. In order to provide this critical information, the NCCN Guidelines Steering Committee has devised a set of Categories of Evidence and Consensus. These annotations contain two dimensions: the strength of the evidence behind the recommendation and the degree of consensus about its inclusion.

Category of Evidence and Consensus	Quality of Evidence	Level of Consensus
1	High	Uniform
2A	Lower	Uniform
2B	Lower	Non-uniform
3	Any	Major disagreement

Category 1: The recommendation is based on high-level evidence (i.e., high-powered randomized clinical trials or meta-analyses), and the NCCN Guidelines Panel has reached uniform consensus that the recommendation is indicated. In this context, uniform means near unanimous positive support with some possible neutral positions.

Category 2A: The recommendation is based on lower level evidence, but despite the absence of higher level studies, there is uniform consensus that the recommendation is appropriate. Lower level evidence is interpreted broadly, and runs the gamut from phase II to large cohort studies (Cook, 1992) to case series to individual practitioner experience. Importantly, in many instances, the retrospective studies are derived from clinical experience of treating large numbers of patients at a member institution, so NCCN

Guidelines Panel Members have first-hand knowledge of the data. Inevitably, some recommendations must address clinical situations for which limited or no data exist. In these instances the congruence of experience-based judgments provides an informed if not confirmed direction for optimizing patient care. These recommendations carry the implicit recognition that they may be superseded as higher level evidence becomes available or as outcomes-based information becomes more prevalent (Baillard, 1993).

Category 2B: The recommendation is based on lower level evidence, and there is nonuniform consensus that the recommendation should be made. In these instances, because the evidence is not conclusive, institutions take different approaches to the management of a particular clinical scenario. This nonuniform consensus does not represent a major disagreement, rather it recognizes that given imperfect information, institutions may adopt different approaches. A Category 2B designation should signal to the user that more than one approach can be inferred from the existing data.

Category 3: Including the recommendation has engendered a major disagreement among the NCCN Guidelines Panel Members. The level of evidence is not pertinent in this category, because experts can disagree about the significance of high level trials (McNeill, 2001). Several circumstances can cause major disagreements. For example, if substantial data exist about two interventions but they have never been directly compared in a randomized trial, adherents to one set of data may not accept the interpretation of the other side's results. Another situation resulting in a Category 3 designation is when experts disagree about how trial data can be generalized. An example of this is the recommendation for internal mammary node radiation in postmastectomy radiation therapy. One side believed that because the randomized studies included this modality (Woolf, 1997), it must be included in the recommendation. The other side believed, based on the documented additional morbidity and the role of internal mammary radiation therapy in other studies, that this was not necessary. A Category 3 designation alerts users to a major interpretation issue in the data and directs them to the manuscript for an explanation of the controversy.

The methodology of NCCN Guidelines presupposes a dynamic process. The NCCN Guidelines may be useful only if the pathways are continuously updated to incorporate new data, and emerging evidence drives the degree of specificity of the recommendations.