MSAC 1054.1 REPORT RESPONSE

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Introduction:

The report MSAC 1054.1 was the third review of treatment using hyperbaric oxygen therapy (HBOT) for soft tissue radio-necrosis (STRN) and non-diabetic chronic hypoxic wounds (NDCHW). It was published on the MSAC website in April 2012 and recommended funding for STRN but not for NDCHW.

The report on NDCHW has some significant failures in process and also in fact and interpretation of fact that make its advice to the Minister incorrect and in fact, with respect to the way and manner in which the cost effectiveness modelling has been done, the outcome (when correctly assessed and calculated) is in fact the opposite to what was reported.

MSAC has reviewed the 1054.1 report produced by itself and the responses are inadequate and do not assess the crux of the issue that the cost effectiveness modelling and the interpretation of data is incorrect and this has directly lead to the results that show that HBOT with usual care is less cost effective than usual care alone.

This report is designed to show both the errors in fact and also how the interpretation of some of the studies is incorrect and assumptions made have no basis in fact and cannot be used to calculate data on behalf of the cost effectiveness study that was performed.

There are also significant issues regarding the process of evaluation of treatments by MSAC particularly when the treatment modality is a secondary treatment and how research requested by MSAC has been disregarded when the results are positive but is used selectively when the issues of funding have been assessed. That discussion is beyond the scope of this document however and as the assessment process has changed (MSAC report 1054.1 was the last report done under the old assessment process), most issues that occurred with the 1054.1 report have probably now been rectified for subsequent reports.

This report will break down each point of contention and has background evidence included as part of the document.

Comparator studies:

The original MSAC1054.1 report stated that

> *"For chronic non-diabetic wounds the most appropriate comparator is usual care."*

(MSAC Report 1054.1, Pg 84)

For efficacy and cost effectiveness there needs to be an appropriate comparator for HBOT to determine efficacy rates. There is an Australian based paper by Gordon *et al* (1) that looks specifically at the cost effectiveness of community based venous ulcer wound care in standard form (ie. in home care) vs a 'Leg Club'. The outcome results of this paper were edited out of the final paper but the original manuscript was provided by Dr Gordon with the cure rates in Table 2 of the manuscript of 20 out of 56 at 3 months (35.7%) and using intention to treat, 25 out of 56 at 6 months (44.6%). This study was done independently of any Hyperbaric Oxygen Facility (so no selection bias) and represents the current level of high quality wound care for venous ulcers. This is comparable to the healing rate of venous ulcers for HBOT of 68.3% at the 6 months assessment point(2).

The comparison relevance was acknowledged indirectly by the MSAC assessment process as it is used by the MSAC 1054.1 report for the figures of costing of consumables in 'usual care' in both groups. Therefore there is acknowledgement and use of a comparator in the Gordon *et al* study and therefore the resultant healing rates should also be applicable.

The Gordon *et al* paper also has the additional issue of bias towards benefitting standard 'usual care' as the clinical pathway for HBOT (discussed later) starts by having usual care for three months *prior* to the person being eligible. Therefore the patients have all failed after three months of usual care (rate 0%) as opposed to the Gordon et al study who had already had healing rates of 35.7% by that stage. So by definition the HBOT patient cohort consist of the 64.3% of patients that are not healed by usual care normally.

This does leave a problem where the patients groups are not compatible by date of assessment. HBOT has measurement points at End of HBOT, 1 month post HBOT, 6 months post HBOT and 1 year post HBOT. This is after 3 months of usual care. This is mitigated and the effects can be compared as the average delay for a patient to enter the ANZHMG woundcare study by Hawkins and Bennett (2011)(2) is **19 months** from the time of the wound developing. The six month comparisons can be made as the wound are not going to heal without specialised care provided by a high risk clinic with best available 'usual care' and the intervention of HBOT.

The way that the MSAC process has managed this with its economic model is that it is treating both standard wound care and HBOT as primary modalities (HBOT is a secondary modality after 'usual' wound care has failed) and when calculating healing rates of HBOT has used the paper by Hawkins and Bennett (2011) and used the healing rates from that paper as the healing rates for standard care.

This is not appropriate as the Hawkins and Bennett paper does not have a comparative 'usual' care arm that can be compared to. The people not allocated for HBOT were due to them

either 1) not having hypoxic wounds and were therefore ineligible or 2) having wounds that had non reversible disease (eg were already gangrenous) and required immediate surgery. So neither of these groups could be considered appropriate for treatment and therefore did not act as a control comparator for HBOT.

The committee of MSAC 1054.1 stated that:

> *"However since there is no common comparator it is not possible to undertake a direct comparison of the data from Hawkins and Bennett (n.d.) and Gordon et al (2006). As a result the data from Hawkins and Bennett formed the basis of the effectiveness of HBOT and usual care for the economic analysis."*

(MSAC Report 1054.1, Pg 87)

By doing this they have **pre-determined the outcome of the intervention without any evidence** and this makes any intervention that is added to the standard care uneconomic regardless of the nature of the intervention.

An example of this would be the addition of antibiotics to a patient with pneumonia in intensive care. If both groups have intensive care and the outcome measure is predetermined as the same for both groups the addition of antibiotics is going to make the antibiotic group less cost effective. However we know that the addition of antibiotics reduces the stay in ICU and increases the healing rate, which makes the addition of antibiotics a more cost effective treatment in the long term.

This is evident when you look at a comparison between the two systems when reviewed at the 6th month point below.

Using the cost numbers provided in the MSAC 1054.1 document (and these are not correct but we will use them as an example) and only adjusting for the rate of healing you end up with the following two economic charts:

PARAMETER	USUAL CARE	HBOT + USUAL CARE	DIFF*.	USUAL CARE	HBOT + USUAL CARE	DIFF*.
COST OF CARE AT 6M	$11747.00	$17670.00	$5923.00	$11747.00	$17670.00	$5923.00
COST OF CARE AT 12M	$40232.00	$42383.00	$2151.00	$40232.00	$42383.00	$2151.00
NUMBER OF PATIENTS	154	154		154	154	
HEALING RATE @6M	0.683	0.683		0.5	0.683	
TOTAL COST PER HEALED PATIENT**	$20776.74	$25504.02	$4727.28	$25989.50	$25504.02	-$485.48
TOTAL COST OVER ALL***	$3199617.96	$3927616.00	**$727998.04**	$4002383.00	$3927616.00	**-$74766.00**

Table 1: Cost comparison using different healing rates but same cost values.

* Diff. = Difference between HBOT + Usual care vs Usual Care. Positive number favours usual care, negative number favours HBOT + Usual care.

** Total cost per healed patient = (Cost of care at 6m x healing rate at 6m) + (Cost of failed care at 12m x (1-healing rate at 6m)) assumes that all cases not healed at 6m go on and do not heal at all

*** Total cost is Total cost per healed patient x 154 (number of patients billed under 13105)

So when the rates of healing are changed to accurately reflect the documented rates of healing at the different time periods, the cost effectiveness of HBOT is obvious. This does not even take into account the fact the that patients in the HBOT cohort are already selected as non-healing with 'usual care' in the first place and the rates of healing with HBOT continue to increase out to the 12 month assessment point.

Clinical vs Economic Model

The MSAC 1054.1 has used two models in its report 1) the clinical model that shows HBOT as a secondary intervention after failure of usual care and 2) the economic model that uses HBOT as a primary intervention.

Figure 1: Clinical model: (MSAC Report 1054.1 Fig 1, Pg 7)

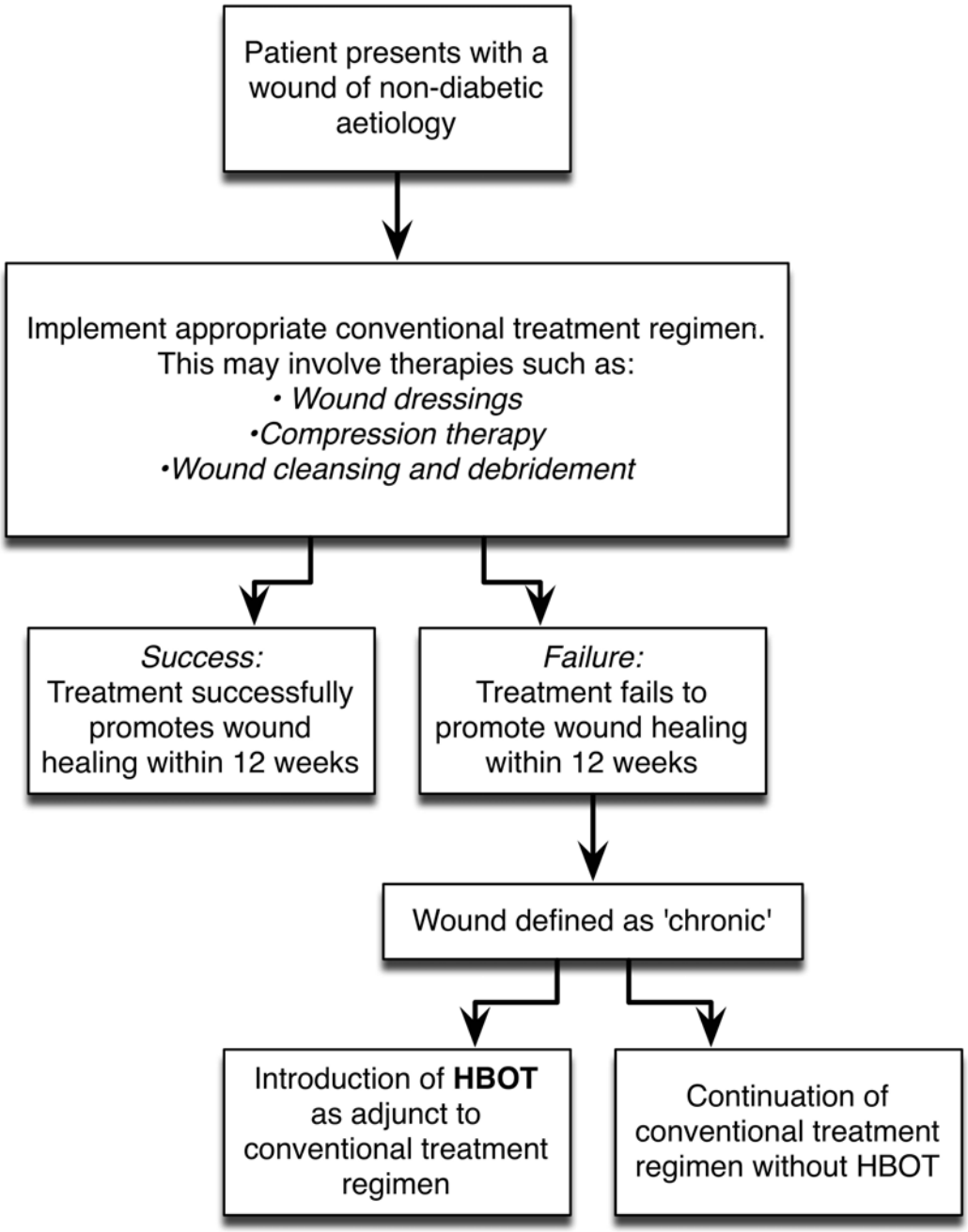
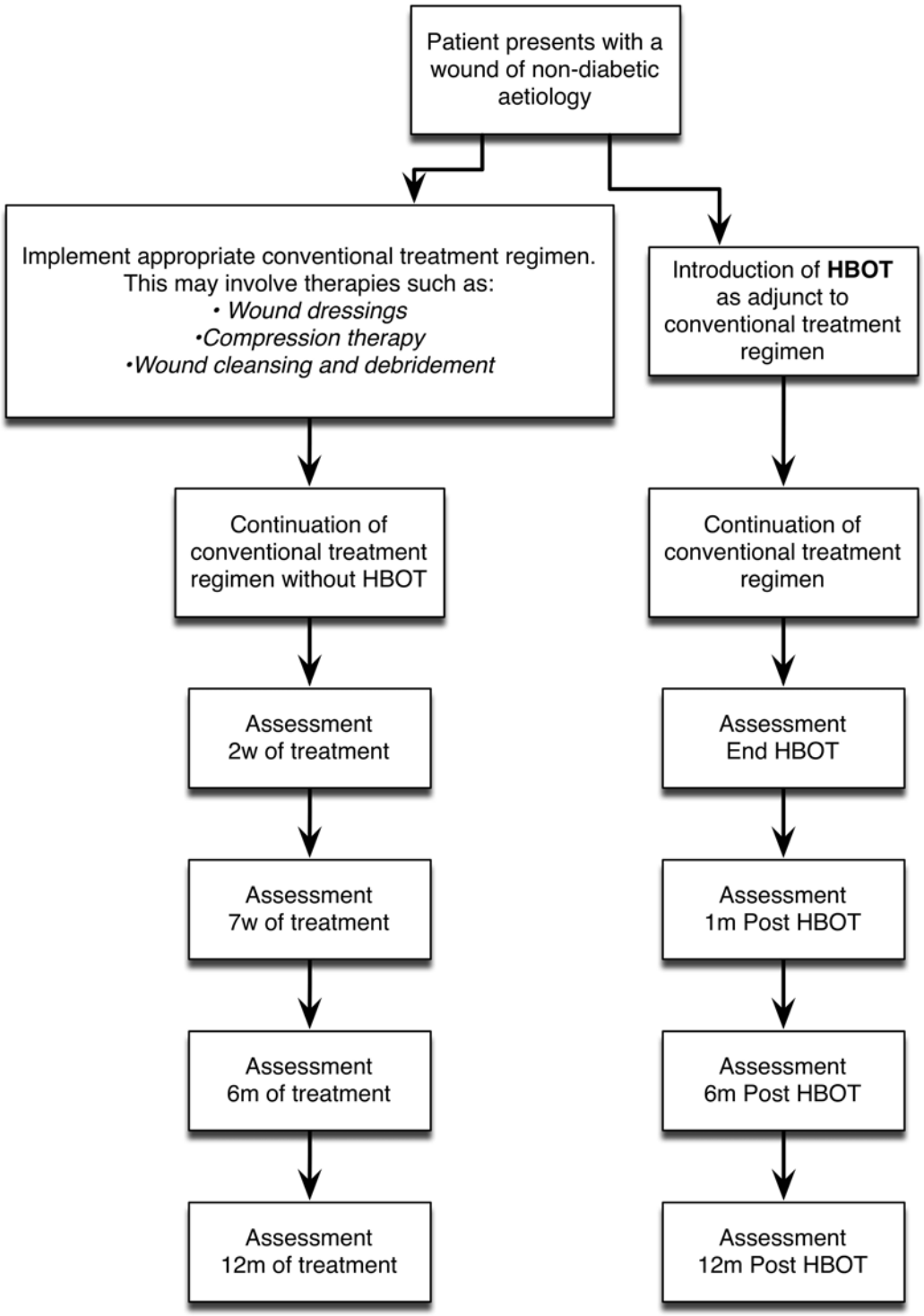


Figure 2: Economic model: Adapted from MSAC 1054.1 Figure 9, Pg 89



What the economic model does not take into account is that 100% of patients that have entered the HBOT stream have already failed conventional treatment (as per study definition with HBOT starting **ONLY** after 3 months of failed conventional treatment) for three months and in fact have failed conventional management for more than 19 months on average.

	RECEIVED HBOT	**NO HBOT**
PATIENTS	355	86
M:F	196:159	46:40
AVERAGE AGE (Range)	69.29y (18-96y)	69.17y (11-94y)
AVERAGE WOUND SIZE (cm^2)	18.20 (s.d. 31.06)	26.90 (s.d. 35.40)
WOUND DURATION (months)	19.94 (s.d. 35.05)	14.32 (s.d. 23.28)

Table 2: Demographics from Hawkins and Bennett (2011)(2)

So the economic model does not take into account the prior 3m which would have a significant impact on outcome as the input is not all patients with wounds BUT all those patients with difficult wounds and the ones that are going to heal with standard treatment are selected out of the group entering the HBOT cohort.

Use of RCT vs Prospective cohort data and interpretation.

After the second MSAC review of HBOT for STRN and NDCHW (MSAC Review 1054 – 2004) an undertaking was made to collate data prospectively and develop a prospective register of patients treated with HBOT and determine their outcome. This was confirmed in a letter from the chairman of the MSAC committee (see Supporting documents) and this was undertaken by the Australian and New Zealand Hyperbaric Medicine Group (ANZHMG) that has published the study in two papers as ongoing research as Hawkins *et al* (2006) (3) and a subsequent follow up paper (2).

This approach was taken because the heterogeneity of the NDCHW is so high that determining the criteria for entry into an RCT would be difficult to establish and the prospective cohort study was thought to be the next best level of evidence and this was agreed by MSAC. When the 3-year review came up, the evidence of the Hawkins *et al* (2006) paper was encouraging but as it was a study that followed people out to a year, the Medicare number was retained under a 3C ruling by the minister so that more data could be gathered. If anything the data from the 6th year of the study (Hawkins and Bennett 2011) is better than the data from the 2006 paper but the results of this were dismissed as they do not reach the level of significance of an RCT.

The only paper that has been determined as an appropriate RCT in the MSAC 1054.1 report was by Hammarlund and Sundberg (1994)(4) which has been interpreted as showing a statistical reduction of wound area at 6 weeks with no difference at 18 weeks.

Surprisingly this is not what the paper itself says. The RCT showed a significant reduction in wound size at week 4 ($p<0.05$) increasing to more significance at week 6 ($p<0.001$) with a large reduction in size of the wound to 64.5% of starting area (vs 97.3% of starting area in the hyperbaric air which in itself is not a placebo). At 18 weeks there was an ongoing reduction in wound size but as stated by Hammarlund and Sundberg:

> *"Although five patients left the study at week 18 (three in the control group and two in the oxygen group), the remaining data indicate a continuing effect on wound healing after the hyperbaric treatment had ceased after week 6.."*

Hammarlund and Sundberg (1994)(5) pg 832.

Statistical analysis was ***not performed*** as the dropout rate did not allow for measurement of the wound area and therefore calculation of size reduction. This is not the same as stating

> *"While the reduction in wound area was greater in HBOT patients at 18 weeks (55.8% compared to 29.6%), this was found to be a statistically non-significant difference.* ***No statistically significant difference was found in the proportion of ulcers healed at 18 weeks in the HBOT group when compared to the placebo treatment, and a pre-planned sensitivity analysis examining the effect of allocation dropouts did not alter the results.****"* [My emphasis]

(MSAC Report 1054.1, Pg 47)

Of those present however all the other oxygen group wounds reduced in size at 18 weeks except for the largest wound, which returned back to pre treatment size.

The MSAC report also states that:

> *'The secondary studies noted that this was a very small RCT in which the randomisation process was inadequately described, concurrent treatments were not reported and only limited patient characteristics were provided.'*

(MSAC Report 1054.1, Pg 46)

Whereas on page 832 of the Hammerlund and Sundberg (1994) paper the randomisation and blinding procedure was spelt out quite clearly including the stratification of patients into age groups <50 years and more than 50 years to remove further confounders.

As these basic facts seem to be incorrectly recorded in the main report, the interpretation of the assessment of the papers must be called into question.

Use of different aetiologies as a pooled result

The calculation of numbers of patients with NDCHW was made off data of Medicare billing of the 13015 item number and percentages of patients treated based on the 2008 Hyperbaric Technicians and Nurses Association (HTNA) reported results of the numbers of NDCHW treated. The problem is that the three aetiological groups that were included in NDCHW in Hawkins and Bennett (2011) have very different treatment regimens and very different healing rates from each other. The rates can be seen in the following graph (with diabetic wounds and the Results from Gordon *et al* (2006)):

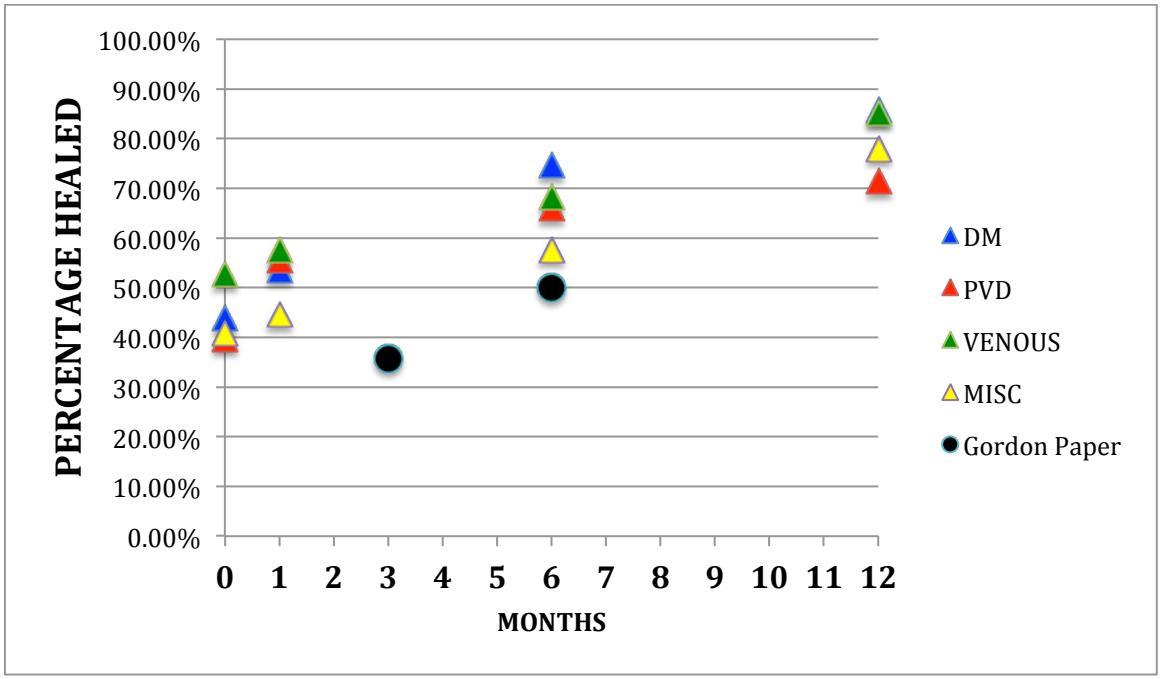


Figure 3: Healing rates from Hawkins and Bennett (2011)(2) and Gordon et al (2006)(1)

DM = Diabetes Mellitus, PVD = Peripheral Vascular Disease (no DM), VENOUS = Venous ulcers, MISC = Miscellaneous ulcers

At 6 months for example the spread of healing rates in the Hawkins and Bennett (2011) paper is approaching 20% difference between aetiologies. They also make up a larger proportion of wounds than venous ulcers (PVD = 25%, MISC =23%, VENOUS = 16%, DM = 36%).

This means that the calculated 154 patients that received HBOT under 13015 only 25% were actually venous ulcers (57/227) and the rest were a variety of aetiologies that may have had differing costs and certainly have different rates of healing. Ultimately, this could have material effect on both the costs and the healing rates.

Miscellaneous

Although the following issues do not have a material impact on the outcome, they do show that there is some concern that things were not checked as thoroughly as would be expected and this may cause a level of concern regarding the calculations that eventually went into the final cost analysis.

1) There are only three **monoplace** chambers available on the ARTG at the time of the report. The fourth chamber is a large **multiplace** chamber **(MSAC 1054.1: Pg 4).**

2) The costing of routine treatments surgical component uses the costing of complications **(MSAC 1054.1: Table 40, Pg 94)** not the costing of surgery **(MSAC 1054.1: Table 39, Pg 93)** but as it is incorrect for both sides, only the total number is elevated not the differential.

3) The statement of potential pathways number 8 is incorrect as it should read:

> *"8. Patients who fail usual care: these patients receive ongoing management + two skin grafts + 12 months community wound care + complications."*

(MSAC 1054.1: Pg 90)

Conclusion

In the MSAC 1054.1 report there are a number of anomalies and errors of fact and interpretation. Also there was a significant lack of clarity regarding what would be considered sufficient evidence which was interpreted by the ANZHMG as a prospective collection of outcome data to 1 year after HBOT (as stated in the 2004 MSAC letter included in Supporting Documents) and which was reinforced in the extension of time to collect further data in 2007 with the extension of the Ministerial 3C ruling to gather sufficient data to be available for analysis in 2010. If it was required in the process to have an RCT, then this would have been performed instead.

Once the data was collected the outcomes of HBOT plus usual care were 'assumed' to be the same as the outcomes of usual care alone with no scientific or evidential basis. All trials to date have shown that the rates of healing of NDCHW have shown a favourable outcome when HBOT is used as a ***secondary*** treatment and this is also verified by the Hammarlund and Sundberg RCT of 1994 which showed a significant effect with only 16 patients randomised into two groups continuing well after the HBOT had finished.

This 'assumption' of equal outcomes as a predetermination means that prior to even assessing the treatment, any additional adjunct treatment cannot be 'cost effective' as it will always cost more than 'usual treatment' alone for the same predetermined outcome. This is not the correct way in assessing any new technology or treatment as a change in outcome rates are what makes a new technology cost effective.

Therefore at worst, HBOT + usual care is as good as usual care alone and is certainly not worse. There is a growing wealth of evidence that when the wound is indolent (in the ANZHMG Study, for 19 months prior to presentation) HBOT can lead to significant healing of the wound, ending the ongoing care and reducing large ongoing costs (not even including severe complications like amputations) into the future while only adding a small initial increased cost (of HBOT) at the beginning.

References

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4. Hammarlund C, Sundberg T. Hyperbaric oxygen reduced size of chronic leg ulcers: a randomized double-blind study. Plastic & Reconstructive Surgery. 1994;93(4):829-33; discussion 34.
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