

## **Homeopathy Research Institute submission to public consultation: 'Natural Therapies Review 2019-20 Membership and Terms of Reference' – Australian Government (Department of Health)**

### **Introduction**

The [Homeopathy Research Institute](#) (HRI) is an innovative charity created to address the need for high quality scientific research in homeopathy.

HRI is dedicated to promoting the evaluation of homeopathy, using the most rigorous scientific methods available, and communicating the results of such work beyond the usual academic circles. We use our resources and expertise to foster new projects and to improve the quality of research being carried out in the field.

HRI's biennial conferences are recognised as the leading event of their kind worldwide, with the academic programme from our most recent conference ([HRI London 2019](#)) providing a platform for presentation of the latest work conducted by 75 researchers from 27 countries.

HRI is recognised as the leading organisation worldwide for representing homeopathy research at an international level.

### **Comment on 'Draft Terms of Reference relating to evaluation of Homeopathy within the Review of the Australian Government Rebate on Private Health Insurance for Natural Therapies 2019-20 (Natural Therapies Review 2019-20)'**

The 'Draft Terms of Reference' (ToFR) state that the Natural Therapies Review Expert Advisory Panel will consider "any additional evidence of [Homeopathy's] clinical effectiveness published since the 2014-15 review or high quality evidence not included in the 2014-15 review to be assessed by the National Health and Medical Research Council (NHMRC)."

There are two inherent problems with this approach that are so critical they potentially render the 2019-2020 Review on Homeopathy meaningless i.e.

- the NHMRC 2015 Homeopathy Review (hereafter 'the 2015 Review') is being taken as a starting point, around which 'additional evidence' will be evaluated, and
- the NHMRC are being given the responsibility of assessing further evidence whilst being under investigation by the Commonwealth Ombudsman facing charges of scientific misconduct, pertaining to the 2015 Review.

## Background on the methodology used for the 2015 Homeopathy Review

The method used in the 2015 Review is best summarised as a Cochrane Overview with unprecedented and scientifically unjustified additional key aspects, including:

- Results expressed as whether ‘reliable’ evidence of effectiveness was found for each health condition, with trials needing to have a **minimum of 150 participants and a quality rating of Jadad 5/5** (or equivalent on other rating scales) to be ‘reliable’.
- Level of confidence (LOC) in the results for each condition was calculated using an ‘**adapted GRADE**’ system which analysed all trials together (despite the fact that they were assessing **multiple different treatments and using different clinical outcomes**) and using **only two criteria** – size and quality – instead of the usual 4-5 criteria.

## NHMRC’s 2015 Homeopathy Review is not a suitable foundation on which to build the 2019-2020 Review

This draft ToFR propose that NHMRC’s 2015 Review will provide a foundation around which ‘additional’ evidence will be considered. This might be a reasonable approach if the evidence included within the 2015 Review had been evaluated in a scientifically robust manner. Regrettably, this is not the case; the methodological flaws in the 2015 Review had such a profound effect on the results that the report’s findings cannot be considered an accurate and objective summary of the included studies and thus the report cannot be used as a foundation for further evaluation of the homeopathy evidence base.

To justify this position, below we present the most striking reasons why the 2015 Review cannot be considered sufficiently accurate or robust for use in this manner:

### 1. Results were determined by an unprecedented and unjustified definition of a ‘reliable’ trial

[Analysis of the Homeopathy Review](#) has established that, of 176 included studies, only 30 trials met NHMRC’s minimum n=150 sample size threshold, and of those, only 5 also met the unusually high minimum quality threshold to be classified as ‘reliable’.

NHMRC’s assessment that **only 5 trials are ‘reliable’** is not apparent when reading the Review because all 176 trials are included and described in the Overview Report. However, when compiling the results table for the public Information Paper (IP p.16-18), the results of **171 trials are effectively excluded** because these trials were deemed to be of ‘*insufficient size and/or quality to warrant further consideration of their findings*’.

It is worth noting that this definition of ‘unreliable’ was applied even to trials with **positive, statistically significant and clinically significant results**; in some instances, the dismissed trials even state that a power calculation had been performed.

## 2. Unprecedented ‘adapted GRADE’ analysis produced invalid LOC assessments

‘GRADE analysis’ is a standardised way of defining the quality of a body of evidence in terms of how confident one can be that an estimate of effect, as detected in the studies, is a true estimate<sup>1</sup>. GRADE is usually used to assess how confident we can be that a treatment is effective **for a particular ‘clinical outcome’**. For this reason, when evaluating a group of trials, **GRADE is usually only used if all the studies being analysed measured the effect of a treatment against the same clinical outcome**. Furthermore, GRADE is usually only used across groups of trials testing **the same treatment**<sup>1</sup>.

For the majority of health conditions identified in the Homeopathy Review there were not enough trials with the same outcome for GRADE to be a suitable assessment tool; neither was there sufficient data for trials to be assessed according to the 4-5 criteria usually used to perform GRADE analysis – only 2 criteria could be assessed per trial.

Although GRADE can be adapted to various clinical questions and scenarios, there are core principles to this method that must be adhered to – most crucially, applying the process to single outcomes and secondly, applying the method to trials testing the same treatment.

The NHMRC did not adhere to these principles, applying their novel method to groups of trials covering **a range of different clinical outcomes** and (in some cases) to trials testing **different homeopathic treatments**. This approach invalidates their level of confidence assessments.

## 3. Inappropriate methodology resulted in a highly inaccurate report

NHMRC identified 57 systematic reviews as being suitable for inclusion, of which they assessed only 7 to be good quality: 4 Cochrane reviews and 3 non-Cochrane reviews. Cochrane is explicit that their Overview method is designed to be used to summarise Cochrane reviews and other good quality reviews only (Cochrane Handbook 2008, Chapter 22, Table 22.1.a - p610), meaning that the method used was only suited to 12 % of the data.

In addition, NHMRC chose not to access the primary studies covered by the systematic reviews (SRs) in order to verify the accuracy of inconsistent data about single studies described in multiple systematic reviews nor to access missing data.

The combination of these elements of NHMRC’s methodology resulted in a poor quality Review with an unacceptable degree of inaccuracy throughout the report (see below).

## 4. Accuracy of quality assessments is unknown for a quarter of the trials

Trial quality, as determined by various quality rating scales, was one of two criteria used for NHMRC’s definition of a ‘reliable’ trial. Despite the direct impact of these quality assessment scores on the Review’s findings, NHMRC did not ensure that this data was accurate.

Instead of accessing the primary studies they decided that, *“If quality of the included studies was not reported in the systematic review then those studies were assumed to be poor*

quality” (IP p.35). Analysis has identified that this rule was applied to 44 out of 176 studies; thus, one cannot know whether their quality assessments for these trials (25% of the data set) are accurate.

## 5. 49 trials are missing due to inappropriate evaluation (22% of the evidence)

NHMRC failed to conduct a literature search for individual trials not captured within systematic reviews, stating that this ‘limitation’ would be compensated for by conducting a public consultation. 49 trials submitted via this route were assessed as being suitable for inclusion. However, none of these trials entered the Overview Report or Information Paper.

The 49 trials were assessed by a different review team and reported on in a separate document ([‘Review of Submitted Literature’](#)). NHMRC’s failure to identify the studies themselves meant this evidence was weakened by being assessed as subject to selection bias, despite this being NHMRC’s own chosen method.

The submitted evidence was also considered in a completely different manner from the main data set of 176 trials: instead of simply asking whether a trial provided evidence of efficacy or effectiveness of Homeopathy for a named clinical condition, the question became, ‘Does this study over-ride the findings of the Overview Report?’. For example, *“Although one small study with low risk of bias favoured homeopathy for the treatment of cough in upper respiratory tract infections, this study did not have enough participants to outweigh the wider body of evidence considered in the overview, which found that homeopathy was not more effective than placebo overall”* (IP p22, referring to Zanasi et al. 2014).

## 6. No literature search for single studies means further data may be missing

NHMRC conducted their literature search in January 2013, capturing systematic reviews which encompassed **primary studies published up to 2010**. However, as mentioned above, this search included **systematic reviews only**, thereby excluding potentially relevant primary studies. Any further exploration of the homeopathy evidence base would therefore require a completely fresh, comprehensive literature search, not just a consultation process requesting submission of ‘additional evidence’.

## 7. Degree of inaccuracies in final Overview Report make it unfit for purpose

Just a few examples of the errors identified in the Overview Report demonstrate that the 2015 Review is not an accurate source of information on the evidence base for homeopathy:

- **Sinusitis** – NHMRC assumed all 3 trials cited were poor quality, when in fact one was high quality and showed homeopathy to be more efficacious than placebo ( $p < 0.0001$ ; 113 participants; Zabolotnyi 2007). 3 further studies are missing from this chapter: 2 are present in other chapters (Ammerschlager 2005 & Steinsbekk 2005) and 1 is missing entirely because it was published in German (Friese 2007).

- **Stroke** – the single study cited in the Stroke chapter (Livingston 1990) is a homeopathy reference book containing no information about stroke, nor any clinical trials on homeopathy
- **Bruising** – one of the two studies cited in the bruising chapter is not a trial of bruising (it is a study on Stroke; Savage 1978) and the data provided about the other study is incorrect (confirmed by checking the original study; Campbell 1976)
- **HIV** – one of the two studies cited is not a homeopathy study (Struwe 1993), but tests the drug Dronabinol (delta-9-tetrahydrocannabinol), the major active ingredient in marijuana given at 5mg twice daily, approved by the FDA for chemotherapy-associated nausea and HIV/AIDS-associated weight loss
- **Allergic rhinitis** – 7 out of 15 trials have the wrong sample size.
- **Psoriasis** – a positive study on psoriasis (Witt 2009) is listed in NHMRC’s 176 included studies, yet no psoriasis chapter exists in the Overview Report.

It is essential that all those involved in planning and executing the 2019-2020 Homeopathy Review are aware of the flaws in the 2015 Review in order to understand why it cannot be used as a foundation for further review work. Further details on this topic, in a succinct format, can be found at [www.hri-research.org/Australian-Report](http://www.hri-research.org/Australian-Report) .

### [Ongoing Commonwealth Ombudsman Investigation precludes use of the NHMRC 2015 Homeopathy Review and further involvement of NHMRC in assessing evidence on Homeopathy](#)

A formal Complaint regarding NHMRC’s Homeopathy Review published in 2015 was submitted to the Commonwealth Ombudsman in August 2016, citing evidence of procedural breaches, conflicts of interest, bias and misreporting on the part of NHMRC. As the Homeopathy Research Institute provided expert input to this Complaint (contributing the scientific aspects of the case) we have an intimate knowledge of both the Review and the investigation.

**It is important to note that the evidence provided in the Complaint against NHMRC met the threshold of merit to trigger a full investigation** which, having taken three years, is now close to completion.

It is hard to see how this report can be used as a solid foundation for further evidence review work until the Ombudsman investigation has been concluded, particularly considering the scientific flaws and inaccuracies in the report (as detailed above) are self-evident to those with experience in conducting evidence reviews.

HRI also seeks clarification as to how it can be considered appropriate for NHMRC to be given the responsibility of assessing the ‘additional’ evidence on homeopathy, whilst this organisation is currently being investigated on charges of scientific misconduct relating to how they assessed the ‘original’ evidence on Homeopathy from 2010-2015.

## Recommended Approach: Health Technology Assessment (HTA)

As the Australian Government is seeking accurate information on which to inform policy making on homeopathy, the most appropriate way forward would be to conduct a **fresh evaluation of this intervention using the Health Technology Assessment methodology.**

This is the most appropriate methodology, being designed to enable ‘evidence-informed context-based decision-making’ (‘Health technology assessment of medical devices. WHO Medical devices series’, World Health Organization, 2011), encompassing the multiple elements decision-makers need to consider, such as safety, efficacy, effectiveness and economic evaluation.

NHMRC claim that a ‘HTA-like’ approach was taken when producing the 2015 Review, yet the methodology used (an Overview of Systematic Reviews) is completely different from the HTA method. Most crucially, the scope of the 2015 Review was far more limited than an HTA, with no assessment at all of evidence pertaining to either safety or cost-effectiveness of homeopathy – both essential aspects Government needs to take into consideration when deciding on the future of rebates.

## The need to include fundamental and basic research

One factor which cannot be ignored when deciding on the final ToFR for the 2019-20 process is the controversial nature of homeopathy. This stems primarily from intense debate regarding the lack of an established mode of action of homeopathic medicines, some of which are diluted beyond Avogadro’s constant during the manufacturing process.

Opinions as to the plausibility of homeopathy inevitably influence how clinical data is interpreted; to eliminate/reduce this ‘plausibility bias’ it is essential to consider basic research (to establish whether there is any evidence that homeopathic medicines can have biological effects) and fundamental research (to determine whether there is any evidence from physico-chemical investigations to support credible hypotheses for the mode of action).

This would provide essential context to the clinical and economic data identified, and be relatively easy to achieve, given the existence of systematic reviews covering these fields.

## Conclusion

The Natural Therapies Review 2019-2020 provides an opportunity to address the shortcomings of the 2015 Homeopathy Review – an issue which has attracted widespread attention and concern, both within Australia and around the world.

Unfortunately, the current plan to evaluate homeopathy as described in the draft Terms of Reference will not achieve this aim; the process would be a waste of valuable Government resources because any further evidence evaluation would be building on a fundamentally flawed foundation, resulting in a meaningless final report.

Given these circumstances, the only way to provide the Australian Government with the accurate information on homeopathy needed to inform policy-making is to carry out a new

evaluation: it is recommended that this evaluation take the form of a Health Technology Assessment, including basic and fundamental research to directly address the debate concerning the mode of action of homeopathic medicines.

### Encouragement to provide evidence to the NTREAP

The public consultation webpage encourages relevant parties to “consider any additional evidence of clinical effectiveness [...] with a view to providing the details of the evidence to the Natural Therapies Review Expert Advisory Panel (NTREAP) when it is established.” The homeopathy sector worldwide would expect HRI to engage in such a public consultation process, however it is unclear how this aspect of the 2019-2020 review is to be conducted. Please can you confirm:

- Submission date
- Guidelines for such submission documents
- That evidence submitted to the NTREAP will not have reduced impact on the review findings due to being assessed as subject to selection bias (as per evidence submitted via consultation during preparation of NHMRC’s 2015 Homeopathy Review)
- Will the review team also be conducting a formal literature search? If so, with what date range, search terms and inclusion criteria?  
If the Australian Government is to conduct a meaningful review that will be accepted at an international level, one would hope and expect that this would involve a sufficiently comprehensive literature search to render public submissions a ‘safety net’ – requested merely to confirm that no essential publications had been missed rather than being relied upon to provide data for inclusion.

The above points are particularly relevant, given that NHMRC’s 2015 Review is not sufficiently robust to be considered reliable; thus in the instance of homeopathy, the ‘additional evidence’ referred to in the ToFR would actually mean the entire clinical evidence base – clearly not a reasonable remit for a public consultation submission.

### Nomination for advisory panel

HRI hereby nominates **Dr Robbert van Haselen** for membership of the Natural Therapies Review Expert Advisory Panel (NTREAP). Although HRI has identified multiple experts who have the required expertise to join the Advisory Panel, Dr van Haselen is the most well-suited candidate for this role worldwide by a substantial margin (see Curriculum Vitae provided).

Dr van Haselen will bring a rare and valuable combination of skills to the NTREAP i.e. expertise in conducting and evaluating evidence of the clinical effectiveness of homeopathy, plus significant experience in the wider field of CAM clinical practice and research. Furthermore, Dr van Haselen is highly respected at an international level.

In anticipation of this nomination, HRI has liaised with Dr van Haselen who has confirmed his willingness and availability to participate. Given the importance of this 2019-2020 Review of homeopathy, Dr van Haselen has offered to cover any additional costs relating to his participation (above and beyond those which would be incurred by an Australian researcher) should this be necessary to ensure that his country of residence does not prohibit his inclusion on the NTREAP.

It is important to note that HRI would have proposed a researcher resident in Australia in the first instance, had a suitable candidate been identified. However, regrettably, there is no researcher in Australia with sufficient relevant expertise to fulfil this role on the NTREAP.

The lack of local homeopathy research experts of this calibre became apparent to HRI some years ago when Australian homeopathy stakeholders contacted HRI to provide expert input on various matters and we have recently confirmed that this situation has not changed – hence our nomination of an international expert.

### Clarifying the role of the advisory panel

Involvement of individuals with suitable expertise is a fundamental requirement of any review process, so it is reassuring to see that the NTREAP will include both a homeopathy research expert and a clinical homeopathy expert. However, the degree of involvement/influence such topic experts would have in the 2019-2020 review process is unclear.

HRI seeks confirmation that the ToFR will ensure that the expertise of the topic experts will **directly inform the review process at all key stages**, from the initial choice of methodology through to analysis of the results and presentation of findings.

Finally, we would like to thank you for the opportunity to submit these comments. We hope this external input will assist in creating an effective review process, enabling the Australian Government to make an accurately informed decision regarding the future of Government Private Health Insurance Rebates for homeopathy.

Kind regards,

A handwritten signature in blue ink that reads 'Rachel Roberts'.

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