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# N-of-1 trials:
## *Building the evidence for natural medicine, one patient at a time*

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### Background

Natural medicine is not included in the Medicare funding model in Australia and is at risk of being withdrawn from private insurance rebates. Indeed this was one of Labor's promises at the last federal election. The recent Review of the Australian Government Rebate on Natural Therapies for Private Health Insurance found that 'overall, there was not reliable, high-quality evidence available to allow assessment of the clinical effectiveness of any of the natural therapies for any health conditions'.[1] The review was limited as it only included evidence from one type of study design (i.e. a systematic review) that had been published in English over the past 5 years.

Yet millions of Australians see natural medicine practitioners every year and two-thirds of Australians use some form of complementary medicines each year.[2] Rates of complementary medicine use are highest in people with chronic diseases and those pursuing illness prevention or health promotion.[3] Surprisingly, this widespread use, particularly in vulnerable populations, is not reflected in government policies. Indeed, it goes largely unmonitored and unregulated, despite criticism that the mixed traditional and scientific knowledge base is inadequate to inform practice. In the face of such wide-scale population consumption, there is a strong imperative for both government and industry support for investigations into the safety and efficacy of natural/complementary medicine. Like mainstream medicine and allied health, natural medicine is increasingly embracing evidence-based practice, and urgently needs to generate high quality evidence to inform practice.

The highest level of evidence for the efficacy of a treatment for an individual patient is findings from a well-conducted N-of-1 trial design. This is a randomised trial with multiple crossovers but with just one patient/participant at a time, so the treatment and outcomes can be tailored to suit the individual. The Oxford Centre for Evidence-Based Practice ranks the N-of-1 trial as level 1 evidence, on a par with systematic reviews of randomised cotrolled trials (RCTs), and higher than the gold-standard clinical trial (i.e. a single RCT) which is classified as level 2 evidence. The idea of designing trials that individualise treatment interventions is consistent with the holistic approach characteristic of natural medicine practice and also new government policy initiatives that seek to promote patient-centred healthcare.

### Significance

In an N-of-1 trial different treatment interventions are compared to find the optimal outcome for the individual patient. This 'trial and error' approach is already intuitively practised by many natural medicine practitioners across the country. Introducing an N-of-1 trial design provides a way of formalising this intuitive approach to capture objective data on measurable outcomes. The outcomes can be determined in collaboration with the patient to ensure that the trial is addressing outcomes that have clinical significance to them.

The results of individual N-of-1 studies can then be disseminated to help guide and inform practice and inspire participation in further N-of-1 trials of natural medicine. In short, if practitioners across Australia were to embrace N-of-1 trials in practice, the field could be transformed by a perpetual generation and incorporation of high-quality level 1 evidence for clinical practice.

We are trialling a program to train natural medicine practitioners to conduct N-of-1 trials in clinical practice. By training and supporting its practitioners to learn how to conduct N-of-1 trials this program could start a grass-roots movement towards the

creation of practice-based evidence in natural medicine.

Building research capacity in natural practitioners will have far reaching effects, including to:

(i) build a solid evidence-base to inform practice for natural medicine practitioners;
(ii) build recognition of natural medicine within the Australian healthcare system;
(iii) support the livelihoods of natural medicine practitioners, and;
(iv) contribute to the health and safety of the Australian population, particularly those with chronic health conditions.

## An example scenario

A naturopath/herbalist may test the efficacy of herbs in hypertension. The client would be borderline hypertensive (i.e. not currently being recommended to take hypertensive medication by their GP but advised that it is likely in the future). The trial would involve the client taking a course of Rosella (Hibiscus rosa sabdariffa) (or other herbal remedy appropriate for that client) for 6 weeks (Treatment A). This may be followed by a washout period (no herbal treatment) for 3 weeks. After the washout period, an alternative herbal remedy (as either a placebo or comparison remedy) could be introduced for 6 weeks (Treatment B). This is followed by another washout period for 3 weeks. This sequence is then repeated, perhaps with Treatment A and B in a different order (the treatment order will be randomised and blinded where possible, in keeping with rigorous clinical trial protocols). The outcome measures could be the difference between the two conditions on BP measurement, a Patient Satisfaction questionnaire or other validated, reliable tool such as Measurement of your Medical Outcome Profile 2 (MYMOP2). The data would be sent back to the research team for further statistical analysis. However, in many scenarios the practitioner will be able to determine whether Treatment A or Treatment B was more satisfactory to the client, simply by asking them.

## Challenges of N-of-1 trials for natural medicine

First, the intervention needs to be thought through for a valid application of the methodology to natural medicine. In traditional N-of-1 trials there has been a stated preference for fast-acting interventions with profound effects and no or minimal washout periods.[4] Natural medicines tend to act more subtly and over a longer term. Secondly, the double-blind conditions mean that, where possible, the practitioner needs to be blinded to the treatment. Finally, chronic stable conditions have been found to be the most suited to N-of-1 trials and the outcomes are change in symptoms of a longer term health condition. We believe these issues can be overcome with some careful planning on a case-by-case basis. We plan to start an N-of-1 service for the natural medicine practitioner community to help practitioners to set up N-of-1 trials in their practices.

## Conclusion

N-of-1 trials can produce high quality evidence to inform natural medicine practice. They can be conducted in real-world clinical settings on actual patients with actual conditions. They have the potential to engage many natural medicine practitioners and to help overcome a perceived limitation of the field - that natural medicine is based more on traditional knowledge than contemporary scientific evidence, by growing the capacity of practitioners to produce high quality clinical evidence to inform natural medicine practice.

### REFERENCES


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