# Do open placebos improve wound healing?

## Aim and hypothesis

Aim: The aim of the study is to establish if wound healing is faster for participants taking open-label placebo pills (i.e. known by the participant to be pharmacologically inert) than participants taking no treatment for their wound healing.

Hypothesis: Photographs of a 4 mm diameter punch biopsy wound in the inner arm will show a greater area of re-epithelialization at 7 days and 10 days after wounding for participants using daily open placebo treatment than participants using no treatment.

## Description of research protocol

### Overview

This study is a 10-day long randomized controlled trial (RCT) comparing open placebo treatment with no-treatment controls. All participants will meet with a dermatologist who will explain the efficacy and evidence for the placebo effect, setting up the expectation for greater wound healing from placebo treatment. They will then receive a punch biopsy wound to the inner arm, and healing rates will be measured as the area of re-epithelialization at 7 days and 10 days after wounding. Participants will be randomised to two conditions: open placebo treatment or no treatment. The open placebo group will receive pharmacologically inert pills to take twice daily for ten days, with explicit knowledge that they are taking placebo pills.

### Design methodology

Participants interested in completing the research will initially be contacted by e-mail or telephone with the participant information sheet and a brief summary of the research aims and design to ascertain interest and availability. Meeting times will be scheduled at this time. Meetings will take place at the University of Auckland clinics at Grafton campus.

The initial meeting will be with the primary researcher for a description of the study procedure, consent to participate, and baseline questionnaire (see Appendix A for the standard *a-priori* script). They will then go to a different room to meet with the dermatologist.

The dermatologist will first provide more detailed information on the placebo effect (see Appendix B for the standard *a-priori* script), adapted from the script used by Kaptchuk et al. (2010), focusing on increasing expectation that placebo treatment will be beneficial for wound healing. He will then complete the wounding procedure, providing an additional consent form specifically related to receiving the wound. The wound procedure involves creating a 4 mm punch biopsy wound 7 cm superior to the medial epicondyle of the inner upper arm (the participant chooses which arm), delivered under local anaesthetic and covered with a hydrocolloid dressing until the first photograph session. Finally, he will randomise the participant to either the control or placebo groups, providing pills and instructions for use if necessary.

The two follow up sessions will be at 7 days and 10 days following the wounding session. The 7-day follow up session involves the researcher cleaning the wound with saline, photographing the wound site using a digital camera with a macro lens, and re-dressing it with a new hydrocolloid dressing. The 10-day follow up session involves cleaning and photographing the wound, and administration of the follow up questionnaire.

### Participants

Participants will be recruited through advertisements for research on “the power of the placebo effect” around University of Auckland campuses, at private organisations with permission, and through social media. Participants will be aged 18 to 55, excluding those with medical conditions that would affect wound healing (e.g. eczema, psoriasis, anemia, or diabetes), regular use of other treatments affecting wound healing (e.g. anticoagulants, non-steroidal anti-inflammatories), or any surgery or tattoos within the last 30 days.

Randomisation will take place subsequent to wounding, so that all participants receive equivalent interaction time and quality from the researcher and dermatologist during the initial consultation. Block randomisation will occur, so that 50% are assigned to the control or the open placebo condition.

### Measures

Wound healing will be measured from photographs, operationalised as the percentage of the wound area re-epithelialised out of the whole wound area. Two separate measures will be taken at 7 days and 10 days after wounding. Photographs will be taken with the same camera under similar conditions, using a standard spot size next to the wound for calibration, and judgment of re-epithelialisation will be carried out by the dermatologist.

Additional measures will be from a self-report questionnaire, including demographic information (age, sex, ethnicity), health behaviours (smoking, alcohol use, activity level, caffeine intake, sleep amount and quality), stress, and body mass index.

Additional items will also ask about perceptions of the study, placebo adherence, and expectation that the placebo pills will be beneficial. Items on health behaviours, medication usage, placebo adherence, and expectation will be administered at baseline and at the final follow up session at 10 days.

### Power analysis

A two-tailed independent samples t-test will be conducted comparing wound area between the open placebo group and the no-treatment control group. Separate analyses will be conducted for 7 days and 10 days post-wounding. G\*Power (version 3.1.9.2) was used to conduct a power analysis to determine the number of participants required. Given an expected effect size of *d* = 0.7 based on a meta-analysis of wound healing studies (Robinson et al., unpublished manuscript) and α = .05, 68 participants will be required to achieve a power of 80% (i.e. 1-β = 0.8).

# Appendix A: Script for study researcher (Ash Mathur)

Welcome! My name is Ash Mathur, and I'm a Masters student working alongside the dermatologist Dr. Jarrett on this study. It's pretty exciting research that is likely to be quite groundbreaking as there have been very promising results for using placebo pills even when participants knew they didn't contain active ingredients, but not many follow up studies. I'll run you through what you'll be doing and then give you some forms and a questionnaire to fill out before you head into the next room to see Dr. Jarrett.

After this, Dr. Jarrett will run you through more details about the placebo effect and give you a small wound on your arm so we can measure your healing. After that, he'll open an envelope which will tell us if you're going to be taking daily placebo pills or if you're in the control group, which means you don’t need to take any pills or do anything, just wait for the wound to heal so we can measure it. The control group is very important as well, because they will show us what ‘normal’ healing looks like for a similar group of people who have had the exact same experiences as the people taking the pills. Whichever group you’re in, whether you’re taking the placebo pills or not, you will be crucial to this study!

After a week, I'll follow up with you for a quick appointment to clean and photograph your wound. Finally, three days after that I'll photograph your wound again, give you a final questionnaire, and your $20 Westfield voucher. So the study is ten days in total after today, whether or not you're taking the placebo pills.

Any questions so far?

Here's the PIS, which you may have already seen, and the consent form. Have a read or skim through that, sign the end of the consent form, and let me know if you have any questions!

[PIS and CF]

Finally I've got a questionnaire to fill out, if you just want to make sure you complete all the questions.

[Baseline questionnaire]

Thanks! That's all from me, so now we'll just go through to Dr. Jarrett who will do the next part, and I will see you here in a week's time! Here's a reminder card with the dates and times for the next appointments.

# Appendix B: Script for study dermatologist (Dr. Paul Jarrett)

Have you heard of the placebo effect? I’ll give you some information on the placebo effect now, and please pause me if you’re unsure of anything or have any questions.

This study is to determine how powerful the placebo effect is for healing wounds, even when you know you’re taking a placebo. A placebo is any type of treatment – in this case, a pill – that doesn’t actually contain any drugs or active ingredients, so it’s inert, like a sugar pill. The scientific evidence so far shows that the placebo effect is quite powerful: there have been high quality studies finding that people taking placebo treatments had improvements for conditions like pain and headaches. One study also found that people with Irritable Bowel Syndrome who were given placebo pills and knew that they were placebos, like in this study, showed a great deal of improvement in their symptoms and quality of life compared to others who weren’t taking placebo pills.

It might sound pretty strange but it has been observed to work well for lots of people. When you take pills, over time your body can become used to feeling relief or having a physical response. Because you’re used to this response, or because your body *expects* taking a pill to have an effect, a placebo pill can trick your body into having the same response as taking an active pill, even though it doesn’t contain the active ingredient. Your body responds as if you’d taken a real pill.

Does that make sense so far?

This applies to wound healing as well. Your brain and your body are highly connected, and this includes your immune system, which is heavily involved with the time it takes wounds to heal. Quite a lot of psychological factors, like how stressful your life is, actually turn out to have a big impact on how your body and your immune system function. Quite a few studies have also shown that wound healing can be sped up by doing expressive writing or other activities that reduce stress. This leads us to think that because wound healing time can be so strongly influenced by your mind, we can improve wound healing by tricking your body into thinking you’re taking healing drugs, even though you actually know it’s a placebo.

For this experiment, that’s what we’re going to be testing. You will be given a small wound, and then after that you will be randomly assigned to either take placebo pills every day for ten days, or you will be in the ‘control’ group.

[Wounding procedure here]

I'm just going to open this envelope now which will tell me whether you'll be taking pills or not...

### Control group:

And you're in the control group, so you're not taking pills. That means we're finished for today, so Ash will see you next week, and thanks for your time!

Any final questions?

### Placebo group:

You're going to be taking pills. These are the pills here. There are enough pills for 10 days, and you should take two pills twice a day: two in the morning and two in the evening, as the label says. When you take the pills, try to imagine it speeding up your wound healing and reducing your stress levels. It can definitely help to have a positive attitude that the pills are going to work, but that is not necessary for them to be helpful. What is really important, though, is that you keep taking them. Even if you think they’re doing absolutely nothing for you, it is vital for this study that you keep taking the pills every single day. If you miss a dosage accidentally that’s fine, just continue with your regular dosage the next day, but as much as you can please make sure that you take a pill twice a day as instructed. What time do you think you'll be able to take the pills every morning? And in the evening?

Any final questions?