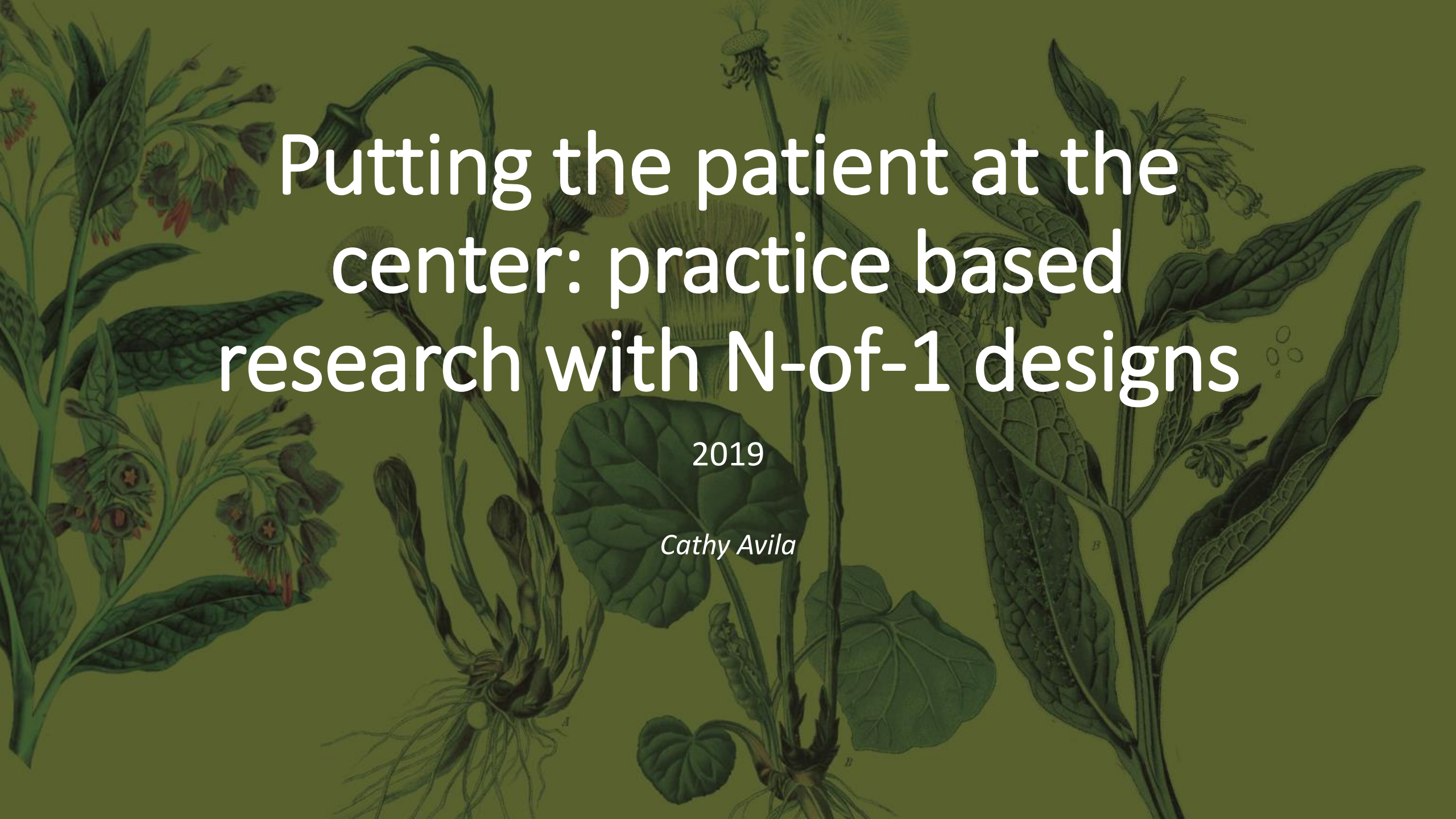


Putting the patient at the center: practice based research with N-of-1 designs

2019

Cathy Avila


Does it do more good than harm?
Is it safe?
How does it compare to treatments known to be effective?
How does it compare to doing nothing?
Does it work?
Is it biologically plausible?

Lessons from the devil's advocate

"Some proponents of CAM try to make us (and often themselves) believe that their therapies are too subtle, too individualised, or too holistic to be squeezed into the 'straight jacket' of reductionist science."

Ernst 2015

- **Biochemical individuality**
- **Individualized medicine**
  - Non-responders or outliers in clinical trails
  - RCT results less relevant/reliable for patients who don't fit the trial profile
    - Complex
    - Polypharmacy

Oxford Centre for Evidence-Based Medicine 2011 Levels of Evidence

Question	Step 1 (Level 1*)	Step 2 (Level 2*)	Step 3 (Level 3*)	Step 4 (Level 4*)	Step 5 (Level
How common is the problem?	Local and current random sample surveys (or censuses)	Systematic review of surveys that allow matching to local circumstances**	non-random sample**	Case-series**	n/a
Is this diagnostic or monitoring test accurate? (Diagnosis)	Systematic review of cross sectional studies with consistently applied reference standard and blinding	Individual cross sectional studies with consistently applied reference standard a blinding		studies, or independent dard**	Mechanism-ba reasoning
What will happen if we do not add a therapy? (Prognosis)	Systematic review of inception cohort studies	Inception cohort studies		r case-control studies, or poor quality prognostic cohort	n/a
Does this intervention help? (Treatment Benefits)	Systematic review of randomized trials or *n*-of-1 trials	Randomized trial or observational stud dramatic effect		case-control storically dies**	Mechanism-ba reasoning
What are the COMMON harms? (Treatment Harms)	Systematic review of randomized trials, systematic review of nested case-control studies, *n*-of-1 trial with the patient you are raising the question about, or observational study with dramatic effect	Individual randomi or (exceptionally) study with drama	ntrolled cohort/follow-up	Case-series, case-control, or historically controlled studies**	Mechanism-ba reasoning
What are the RARE harms? (Treatment Harms)	Systematic review of randomized trials or *n*-of-1 trial	Randomize or (except study wit			
Is this (early detection) test worthwhile? (Screening)	Systematic review of randomized trials	Rando	ort/follow-up	Case-series, case-control, or historically controlled studies**	Mechanism-ba reasoning

*** Level may be graded down on the basis of study qu studies, or because the absolute effect size is very s**

**** As always, a systematic review is generally bet**

How to cite the Levels of Evidence Table
OCEBM Levels of Evidence Working Group*. "The Ox
Oxford Centre for Evidence-Based Medicine. http://

- Systematic Review of RCTS
- N-of-1 study for an individual
- Randomised Controlled Trials
- Cohort
- Case study
- Animal studies
- In vitro

Are the effects of an intervention clinically relevant?

Randomised control trials and N-of-1 designs – the same, but different

Cross-over designs

Each participant takes both the active intervention and the placebo intervention

Randomised clinical trial: participants are randomly assigned to take either intervention A or intervention B first.

Intervention A	Washout	Intervention B

N-of-1 design: one participant is exposed to each pair of interventions on more than one occasion in a random order

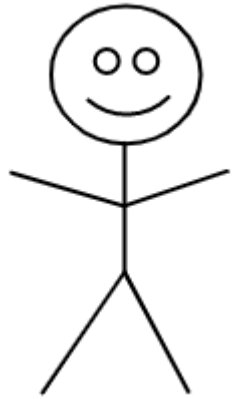
A	Wash out	B	Wash out	B	Wash out	A	Wash out	A	Wash out	B

Double blind Placebo controlled Randomised Clinical Trial

- **Benefits**
  - Increases the body of evidence for a herb or other intervention
  - Increase the body of evidence regarding safety

N-of-1 design

- **Benefits**
  - Informs clinical decisions for a patient and practitioner
  - Increases confidence in a regime
  - Increases the body of evidence for a herb or other intervention
  - Increase the body of evidence regarding safety



Double blind Placebo controlled Randomised Clinical Trial

- **Designed by researchers** to answer a question about
  - The efficacy of a particular herb or other intervention
  - Compared to placebo or usual treatment
  - In participants with a defined condition
  - At a dose chosen for its potential to safely produce an effect, based on the literature

N-of-1 design

- **Designed by the practitioner and patient** to answer a clinical question about
  - The efficacy of a specific treatment (intervention) or treatments for the patient
  - Compared to placebo, usual treatment or another treatment
  - In their current state of health
  - At a dose guided by clinical experience with the patient, research or general clinical experience and discussed with the patient.

Double blind Placebo controlled Randomised Clinical Trial

- **Blinding**
  - Neither the participants
  - Nor the research team, including assessors
  - know which intervention is being taken by the participants until the analysis is complete.

N-of-1 design

- **Blinding**
  - Neither the patient
  - Nor the practitioner researcher, including assessors,
  - know which intervention is being taken until the analysis is complete.

- How do we know if an intervention is working?
  - The outcome of the intervention is measured, classically at the start and the end of a study
    - Outcomes measures depend on the aim of the research
      - Examples: pain, frequency of coughing episodes, sputum colour, self-esteem, blood pressure.

Double blind Placebo controlled Randomised Clinical Trial

Outcome measurements

- Relevant to the research question
- Reliable, validated
- Affordable
- Realistic for the participants

N-of-1 design

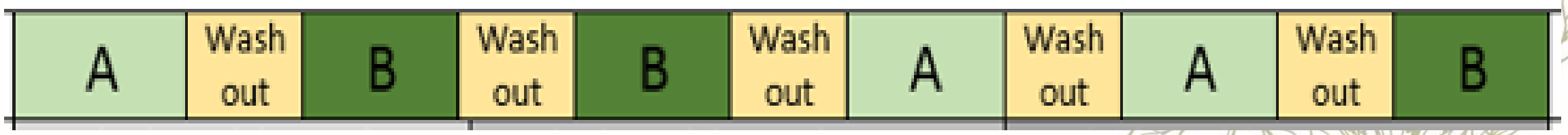
Outcome measurements

- Relevant to the patients condition and concerns
- Reliable, validated
- Affordable
- Realistic for the patient

Cross-over designs

Randomised clinical trial: the greater the **number of participants** the greater the reliability of the data and the better able the study is at predicting the effect on a patient in clinically relevant ways.

N-of-1 design: the greater the number of times a **symptom or sign is measured** during each period of the study the more accurate and reliable the results.



Measuring perceptions (pain, colour, sensation, emotional state)

- Use questionnaires (aka instruments, tools)
- Validated questionnaires are the best choice
  - Validated means a questionnaire has been shown to measure what it claims to measure
  - ‘Rate your pain from 0-10’

Table 1.

Indiana Polyclinic Combined Pain Scale

Rate your pain according to the following scale

		Examples	
0	**No Pain**	No pain	0
1	**Unpleasant Sensation** - An occasional uncomfortable feeling. Almost no limit to function	Mild skin irritation	1
2	**Minimal** - Pain frequently brought to one’s attention but acceptable. Able to engage in pleasures of life with some interference. Causes to avoid rigorous activities.	Small bruise	2
3	**Mild** - Tolerable, but unsettling and on one’s mind. Interferes with pleasures of life. Stops some productive activities.	Scraped knee, Jammed finger	3
4	**Mild to Moderate** - Only short intervals of comfortable function; sometimes interrupts Activities of Daily Living, such as bathing and clothing and regularly prevents involvement in many tasks outside of the home. Decrease in job performance.	Major bruise, Ankle sprain	4
5	**Moderate** - Pain constantly on one’s mind; decrease in concentration, job performance and noticeably decreased enjoyment of life. Frequent missed work / time off. Cannot perform normal tasks without an increase in pain.	Moderate toothache, Headache for days	5
6	**Moderate to Severe** - Significant limitations of Activities of Daily Living; productive activity/work is nearly impossible. Hard to do anything, but think of pain and ER visit.	Day after major surgery pain	6
7	**Severe** - Difficulty doing more than basic chores; pain prevents productive activity. Frequent crying; pain is impossible to tolerate for long period of time without going to the ER.	Stabbed with a knife, Broken leg	7
8	**Debilitating** - Causes uncontrollable moaning and distress and completely impairs productive activity. Cannot be still, can’t maintain a reasonable conversation. It is impossible to “put on a good face.” Emergency medical attention is required.	Natural childbirth, Small kidney stone	8
9	**Agonizing** - Individual cannot function; uncontrolled screaming and tearfulness. Emergency medical attention is required and hospitalization is recommended.	Arm burning in a fire, Large kidney stone	9
10	**Worst Imaginable** - Paralyzing; person is in and out of consciousness and near death as a result of the pain. Emergency medical attention *and* hospitalization are required.	Being torn apart while still alive	10

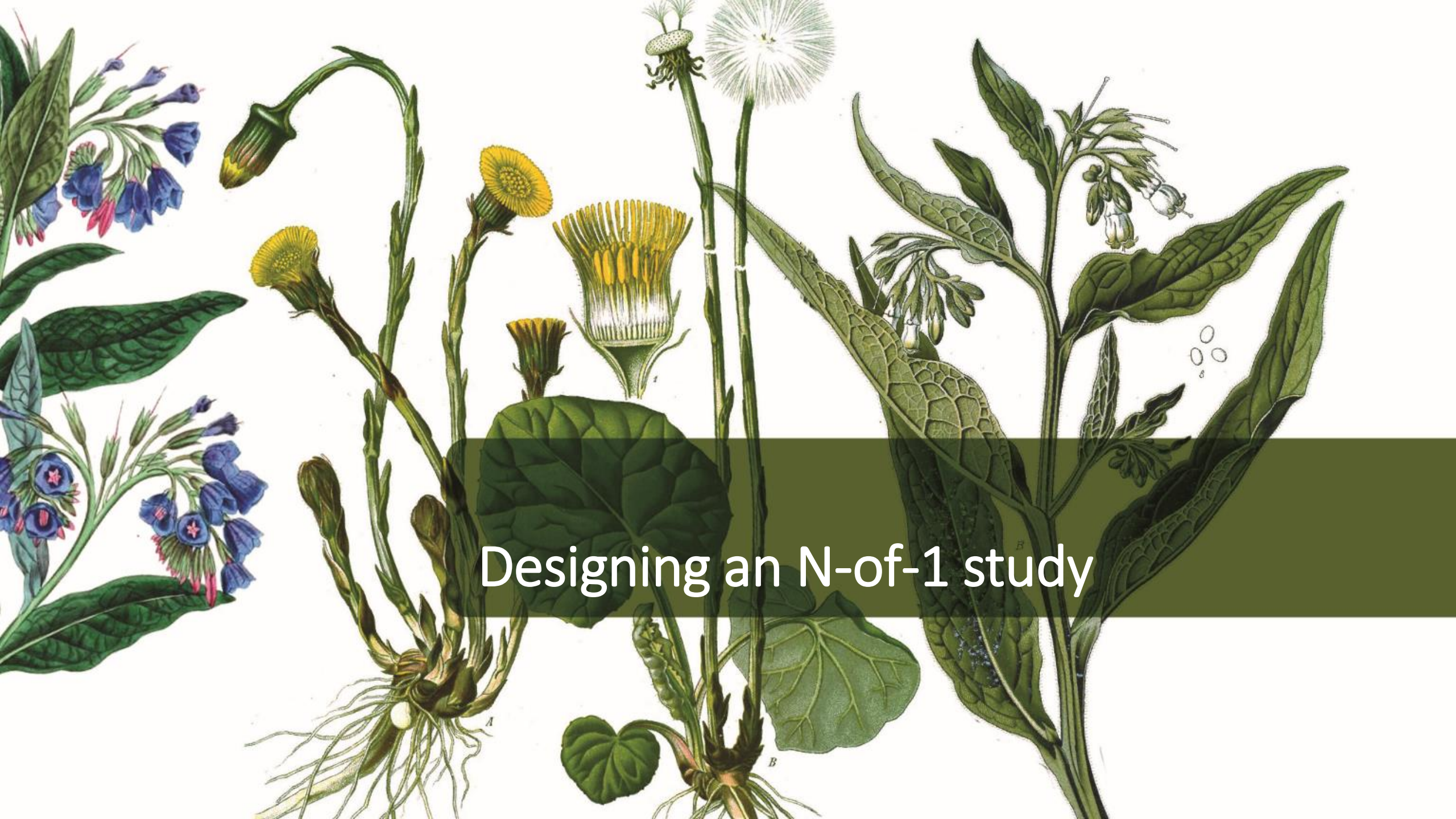
https://www.practicalpainmanagement.com/sites/default/files/chapter4a-table1.pdf

Double blind Placebo controlled Randomised Clinical Trial

- **Control of variables**
  - Characteristics of the participants carefully specified
    - e.g. medical diagnosis of early stage emphysema
    - Not pregnant or lactation
  - Specify age range
  - Exclude people who will add extra variability
    - E.g. people with other pre-existing conditions
    - people taking certain medications, CM products

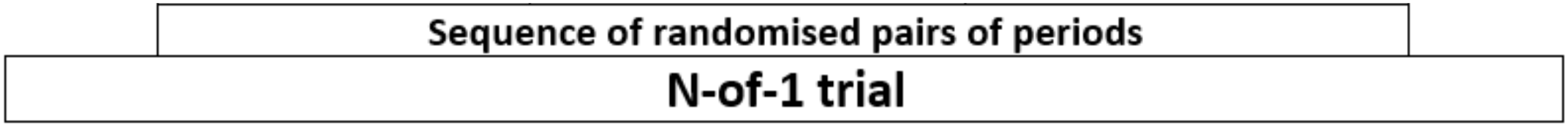
N-of-1 design

- **Control of variables**
  - Can accommodate any patient
  - How variables are controlled for is negotiated with the patient
  - Tailored to neutralise factors known to aggravate or alleviate the condition

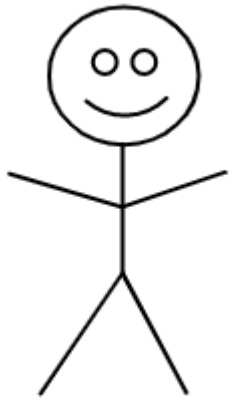


Designing an N-of-1 study

Overview of an N-of-1 trial design



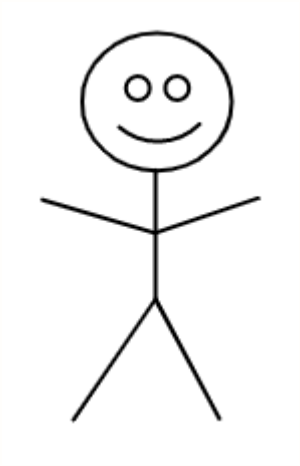
N-of-1 trial design



Intervention A	Washout	Intervention B
• A simple or single herb • A tonic with several herbs • A placebo (needs to match in taste, colour and smell)		• Another simple or single herb • A tonic with a different mix • A placebo (needs to match in taste, colour and smell)

The patient takes both the interventions during the trial.

Why and when a washout?



Intervention A	**Washout**	Intervention B

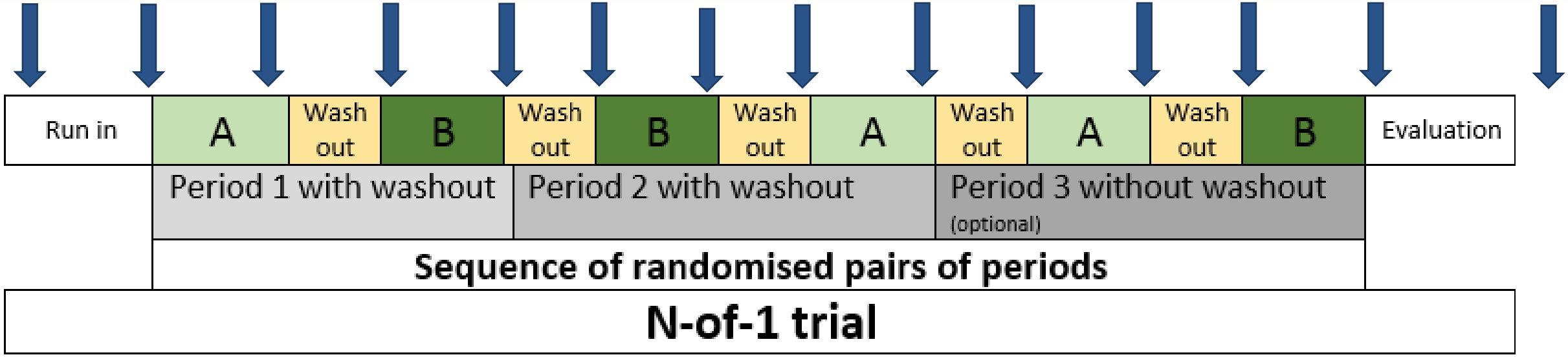
Do you expect the herbs to have a lasting effect?

- **Short term action**, as in pain relief. **No wash out**.
- **Long or medium term action**, such as a tonic action, **wash out** before starting the second intervention.
- Duration of the washout – research/clinical experience

Outcome measures in N-of-1

- Daily diary
- Patient perception
  - Patient Perceived Symptom Scale
- Validated questionnaire used in randomised control trials of similar conditions
  - Increases the rigour of the design
  - Allows comparison of the results
- Objective measures
  - Safety bloods
    - liver function test
    - full blood count
    - urea electrolyte creatinine
  - Monitor lung function, blood pressure, stool samples, Lipid panel etc.
  - BMI, waist circumference etc.

Measurement time points



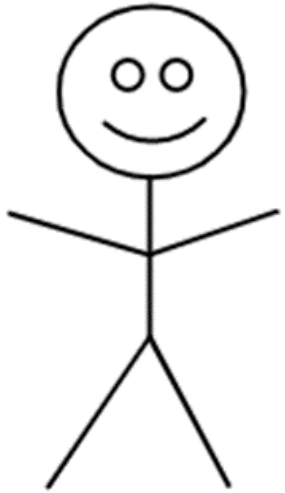
Analysis

Double blind Placebo controlled Randomised Clinical Trial

- **Analysis**
  - Specialised knowledge and software
  - Descriptive statistics
  - Non-parametric and parametric statistics

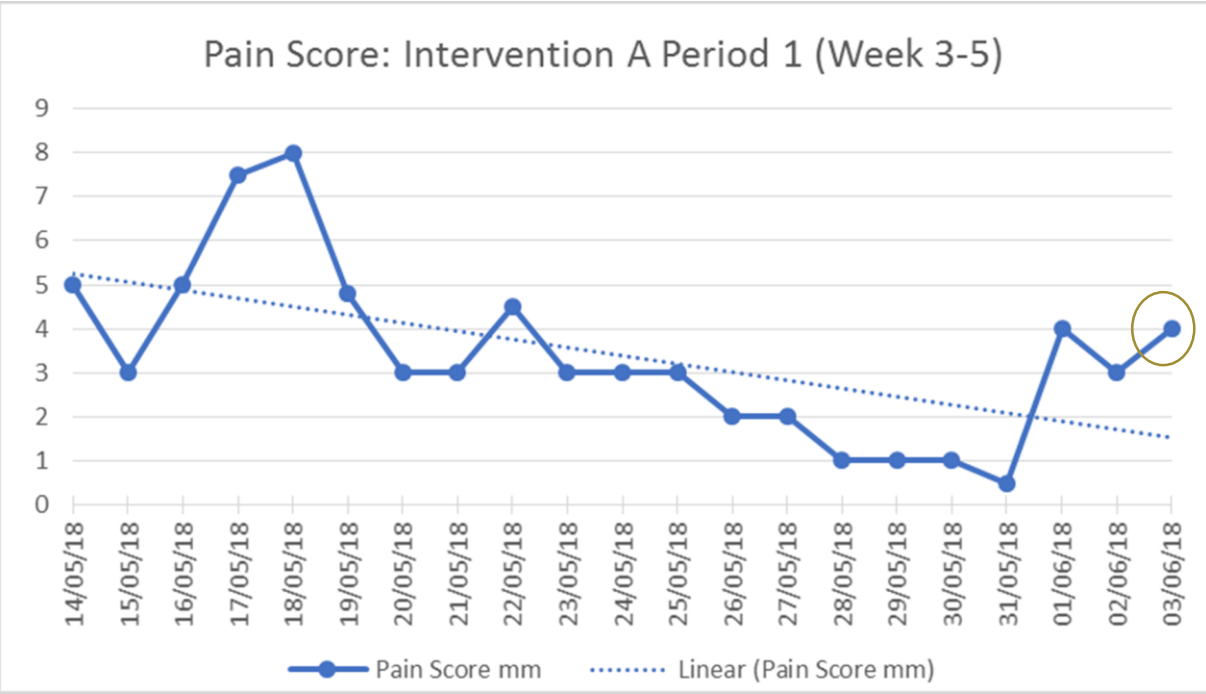
N-of-1 design

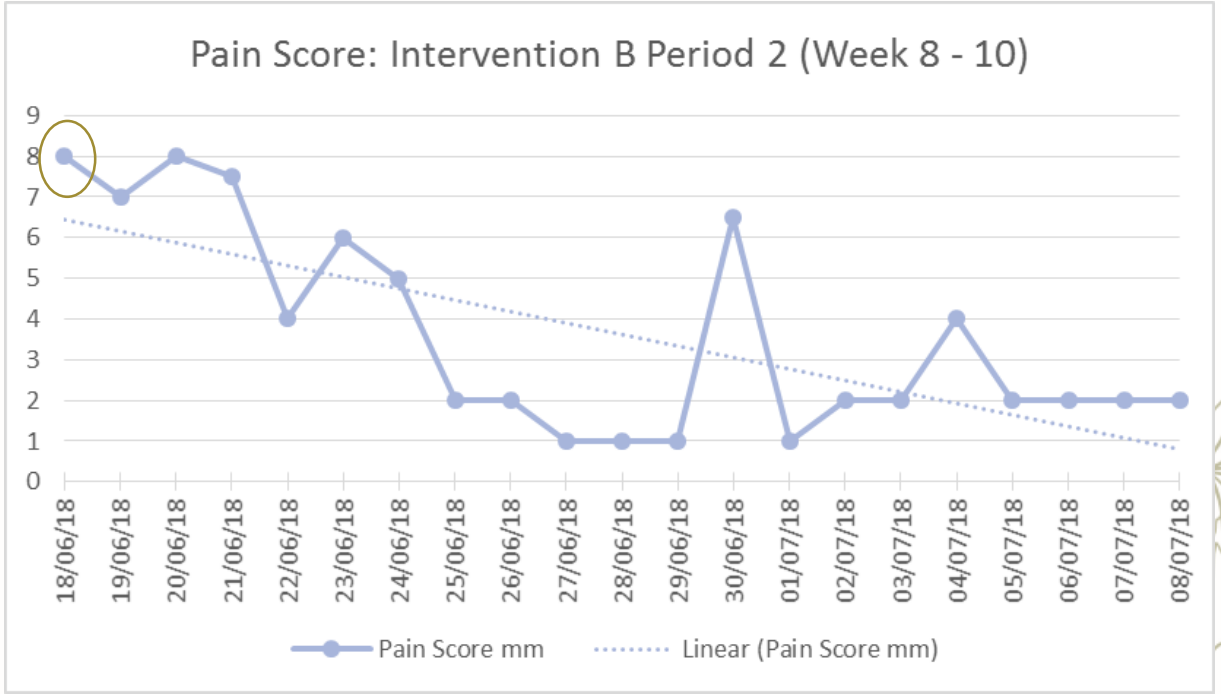
- **Analysis**
  - Excel spreadsheet and patience
  - Visual analysis
  - Simple descriptive stats
    - Means (averages)
    - Ranges
    - Comparisons



Daily pain ratings for intervention A and intervention B

Wash out: weeks 6 and 7



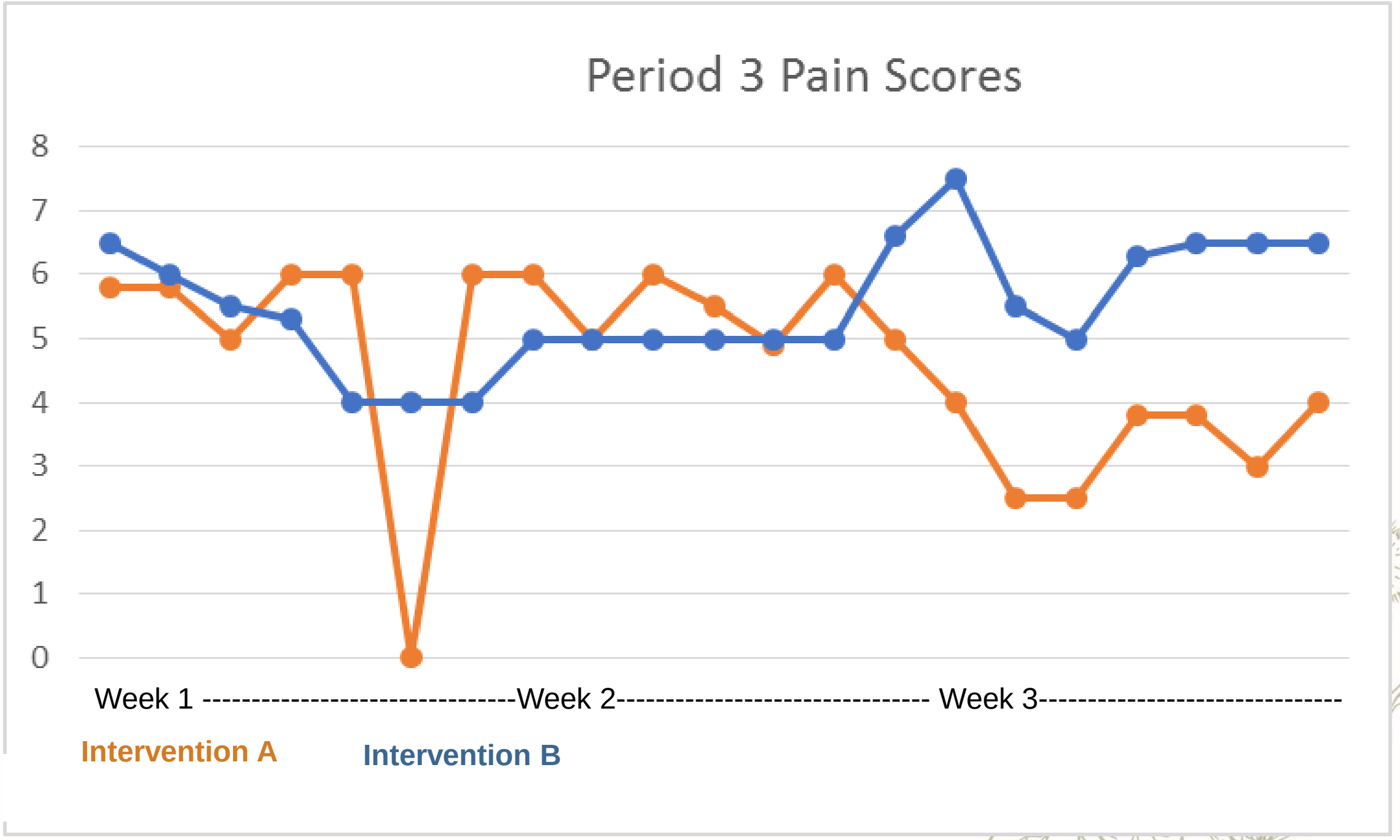


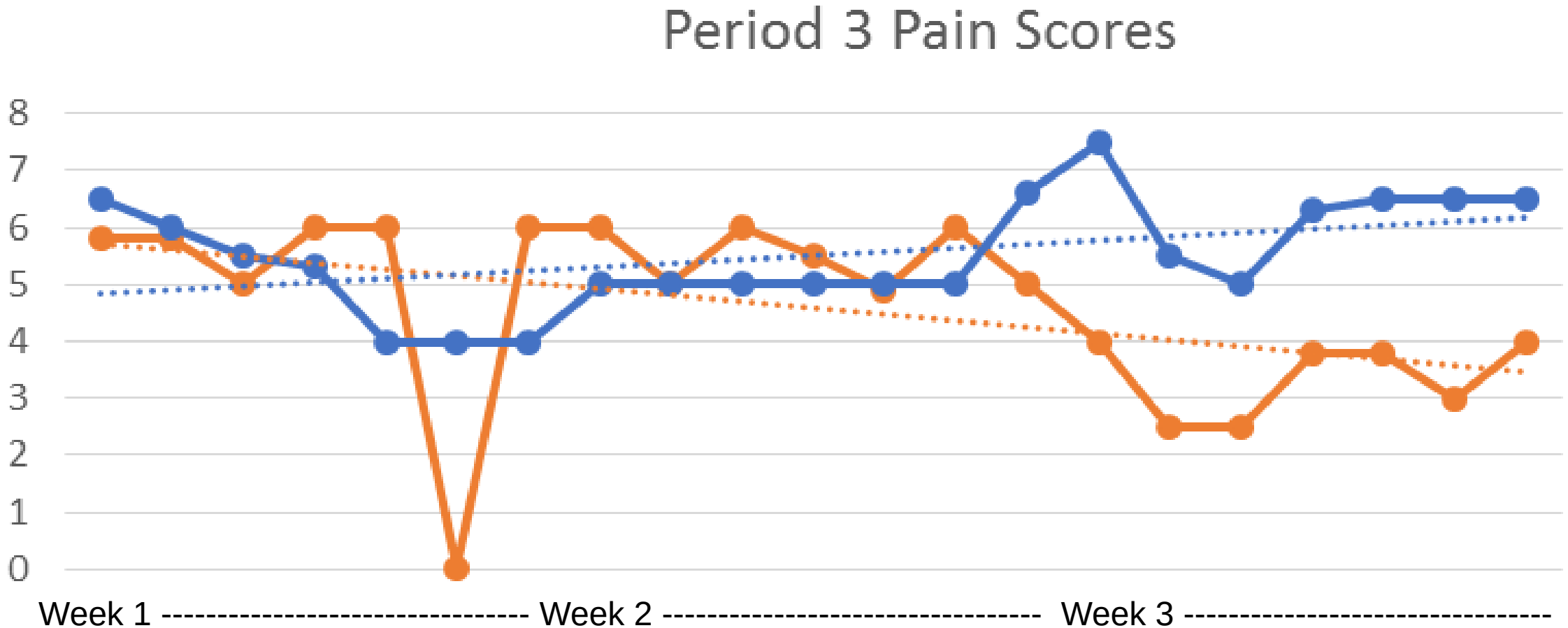
Compare Period 1 and Period 2 scores:

- Mean
- Worst day score
- Best day score
- Range

Was the wash out needed?
Did the washout work?

- Compare the last day before wash out with first day of next period


Period 3 Pain Scores
8
7
6
5
4
3
2
1
0
Week 1 ----------Week 2---------- Week 3----------
Intervention A
Intervention B


Period 3 Pain Scores
8
7
6
5
4
3
2
1
0
Week 1 ---------- Week 2 ---------- Week 3 ----------
Intervention A
Intervention B
Trend lines

Practitioner researchers in a collaboration

- Support with
  - Trial design
  - Ethics application
  - Trial registration
  - Funding streams

Spreading the word

Double blind Placebo controlled Randomised Clinical Trial

- **Dissemination and translation**
- Peer reviewed journals
- Professional journals, conferences, social media
- Informs about efficacy of the specific herb or other intervention
- Informs on the safety of the herb in relation to a specific dose and duration of use
- May be reanalysed in a systematic review with like studies
- LIMITATIONS
  - Evidence is approximate for the many potential patients
  - Time consuming
  - Extremely expensive
  - Often designed to meet industry posed

N-of-1 design

- **Dissemination and translation**
- Inform clinical decision for the individual patient
- May be written up and published in a peer reviewed journal
- Professional journals, conferences, social media
- Potential to be re-analysed together with other N-of-1 studies using the same methodology and herb for the same condition
- LIMITATIONS
  - Rigorous methodology takes time to plan and execute
  - Support from an academic institution (and usually, from academics) required if aim to publish and add to the evidence base

Practice based evidence using N-of-1 designs

- Patient first
- Safety
- Clinical efficacy
- Independent evidence
- Philosophical integrity
- Ethical

Rigorous design

Thank you!

Any questions?