Alternative (fixed) trial designs

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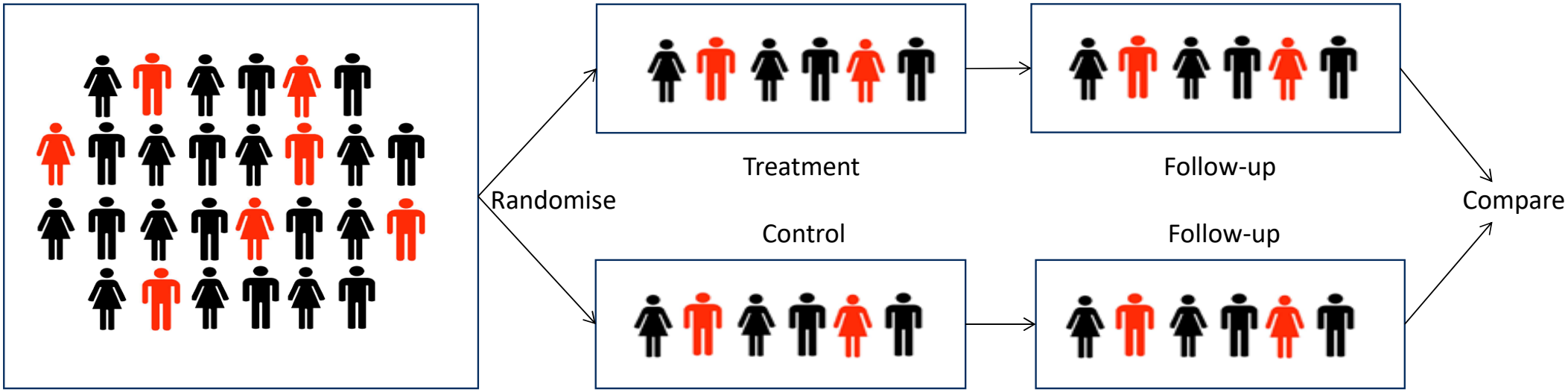
Overview

- Crossover trials
- Cluster randomised trials
- Cluster-crossover trials
- Stepped wedge cluster randomised trials
- Factorial designs
- Summary

Individual level, fixed, RCT



Aim: To compare some outcome measure between treatment and control groups

e.g. Compare the risk of death or severe disability nine months after randomisation between adjunctive treatment with dexamethasone or placebo.

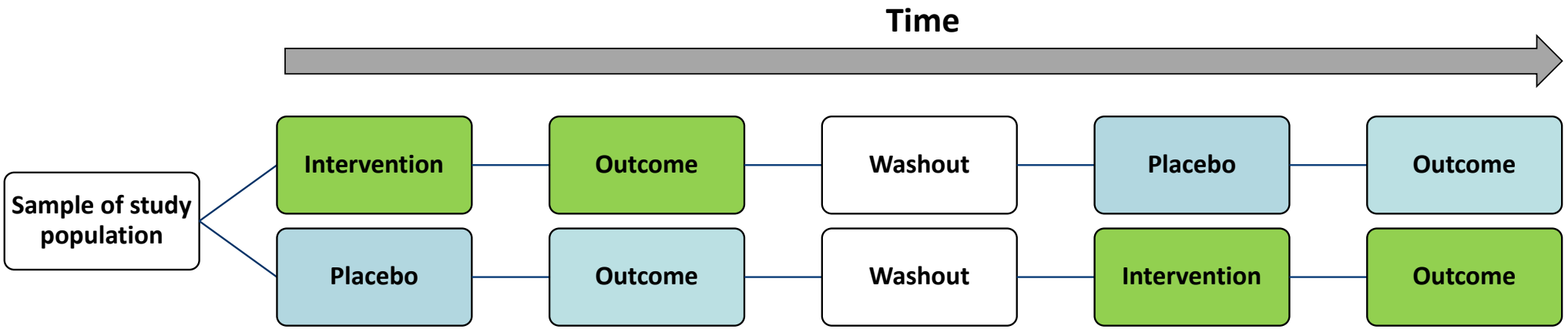
Cross-over trials

CONSORT 2010 statement: extension to randomised crossover trials
Dwan K et. al. BMJ 2019

- Extends 14 items of the CONSORT statement

Cross-over trials

- Each individual participant receives two or more interventions and acts as its own control – *that is a within-individual comparison*
- Initial randomisation followed by crossover to the other intervention
- Individuals are randomised to order of interventions



Cross-over trials: an example

Population – Children with cystic fibrosis

Intervention – Azithromycin

Control – Placebo

Outcome – Forced Expiratory Volume (FEV) in 1 second

Participants randomised to sequence:-

AB – Azithromycin(A) then placebo(B)

BA – Placebo(B) then Azithromycin(A)

Equi et al. Long term azithromycin in children with cystic fibrosis: a randomised, placebo-controlled crossover trial Lancet 2002;360:978

Cross-over trials: an example

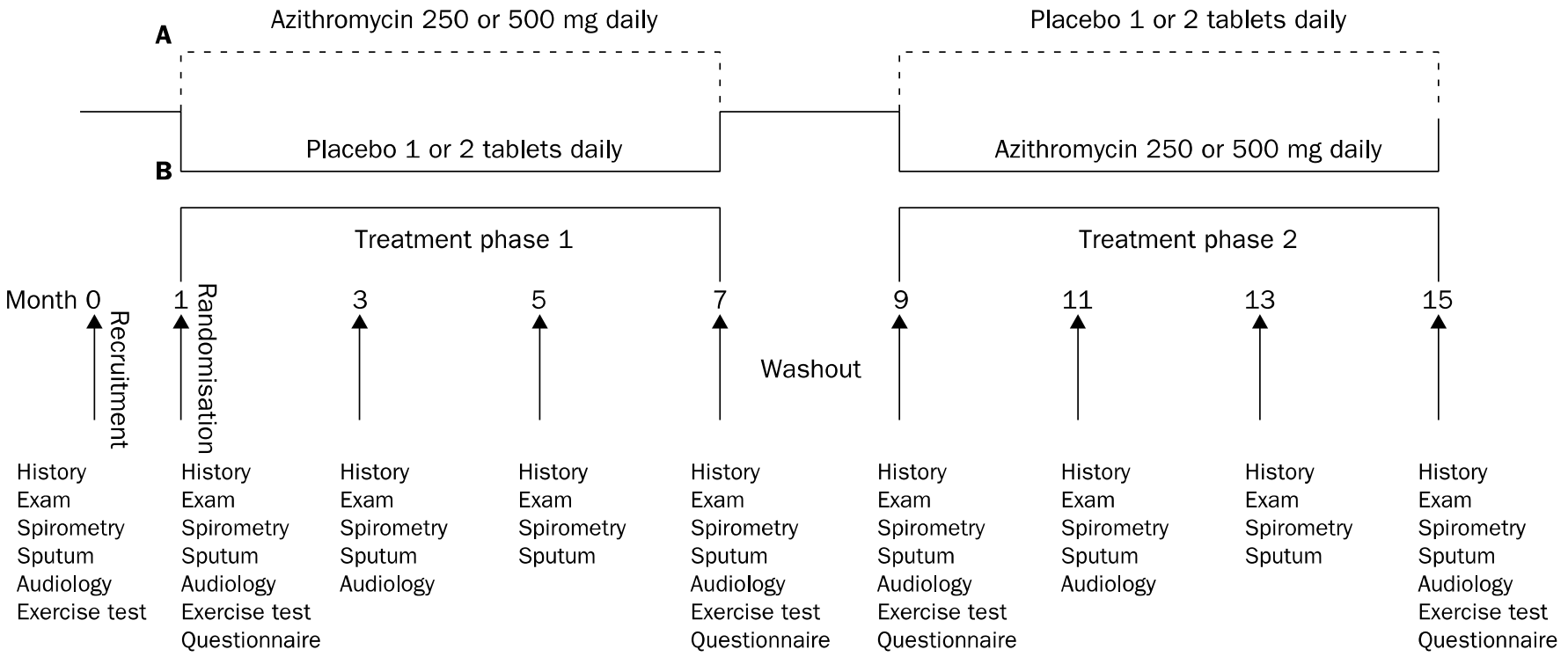


Figure 1: **Study protocol**

Equi et al. Long term azithromycin in children with cystic fibrosis: a randomised, placebo-controlled crossover trial Lancet 2002;360:978

Cross-over trials

Pros

- Within-individual comparison - variability of outcome for treatment effect reduced because less variability within- than between-individuals
- Fewer participants needed than a parallel group design

Cons

Carry over effect of the intervention (*design assumes minimal carry over effect*)

Participants drop out after 1st treatment and don't receive 2nd treatment

Generally, only suitable for

- participants with conditions or diseases that are chronic or relatively stable
- short-term outcomes
- interventions with short term impact, so washout period is feasible

Quiz??

An investigator comes to you with a research question they would like to investigate, see the PICOT below.

Would a cross-over trial be appropriate/feasible?

Yes or No

Population	Patients with tuberculosis meningitis
Intervention	Dexamethasone plus standard treatment
Comparator	Standard treatment
Outcome	*Death*
Time	9 months follow-up
(study design)	??

Quiz??

An investigator comes to you with a research question they would like to investigate, see the PICOTs below.

Would a cross-over trial be appropriate/feasible?

Yes or No

Population	Patients with chronic artery disease
Intervention	85 gms of almonds daily plus NCEP step 1 diet
Comparator	NCEP (National Cholesterol Education Program) step 1 diet
Outcome	Blood pressure
Time	Outcome measured at end of 6 week intervention/control
(study design)	??

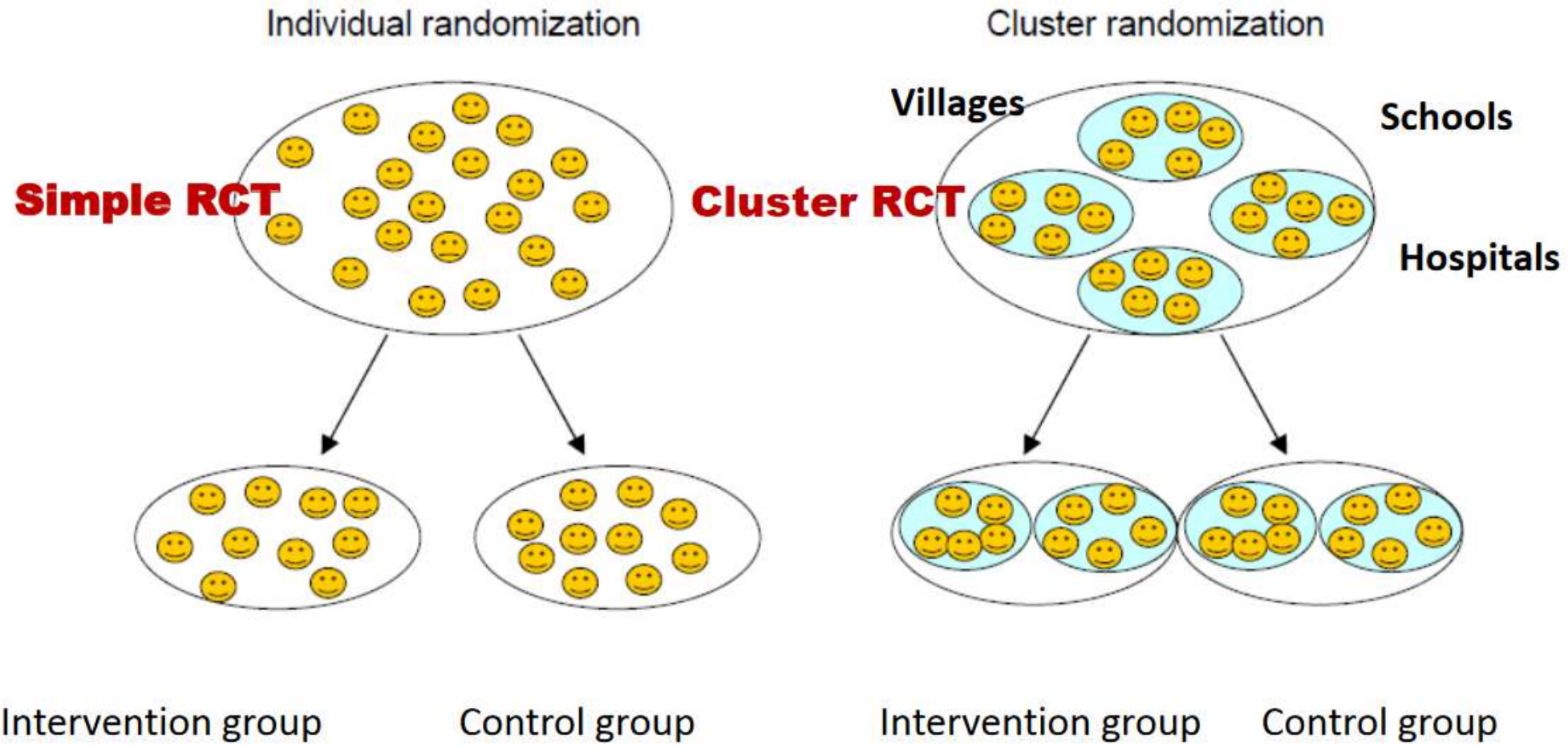
Cluster randomised trials

CONSORT 2010 statement: extension to cluster randomised trials
Campbell MK et. al. BMJ 2012

Key features of statement

- Rationale for adopting cluster design
- Incorporation of clustering into sample size estimation and analysis
- Chart showing flow of clusters through the trial, from assignment to analysis

Randomisation in a cluster RCT



Source: (Fig) https://www.stata.com/meeting/india13/materials/in13_bharti_s.pdf

Cluster Randomised Trials: *Rationale*

Cluster randomised trials are experiments in which **clusters of individuals** (e.g. schools, villages, general practices) rather than independent individuals are **randomly allocated** to intervention groups

Potential reasons include:

- Intervention naturally applied at the cluster level *(e.g. Effect of water and environment revitalisation in informal settlements in Indonesia and Fiji (RISE))*
- To avoid treatment group contamination *(e.g. education program vs usual care to patients in a general practice)*
- Applying the intervention at the cluster level is more feasible than at the individual level *(e.g. intervention at a school)*
- Ethical considerations
- To enhance participant compliance

Cluster Randomised Trials:
Incorporation of clustering into sample size

Unit of randomisation: cluster

Unit of outcome measure: individual

- Observations on participants in the same cluster tend to be correlated *(intracluster correlation)*
- Sample size for a cluster randomized trial needs to be greater than an individually randomized trial
- Sample size needs to be inflated by 'design effect' which depends on intracluster correlation and average cluster size. *(Note, it is better to have a large number of clusters with less participants per cluster, than a small number of clusters with many participants per cluster)*

Cluster Randomised Trials:
Conduct & analysis

- Clusters are usually randomised all at once

- Prior consent to randomisation
  - Yes for consent at cluster level
  - Often not possible at the participant level, and participants can only be asked for consent to receive the intervention to which their cluster group has been assigned

- The analysis of outcome measures at the individual participant level need to take account of clustering

Cluster randomised trials

Pros

- Evaluates interventions that are delivered at cluster level
- Avoids contamination of the intervention to individuals not randomised to the intervention
- Increases feasibility and participant compliance for some interventions

Cons

- Sample size needs to be increased by design effect (intracluster correlation & number of individuals per cluster)
- Large number of clusters required
- Potential imbalance between intervention arms (*randomising at cluster level*)

Quiz??

An investigator comes to you with a research question they would like to investigate, see the PICOT below.

Would a cluster randomised trial be appropriate/feasible?

Yes or No

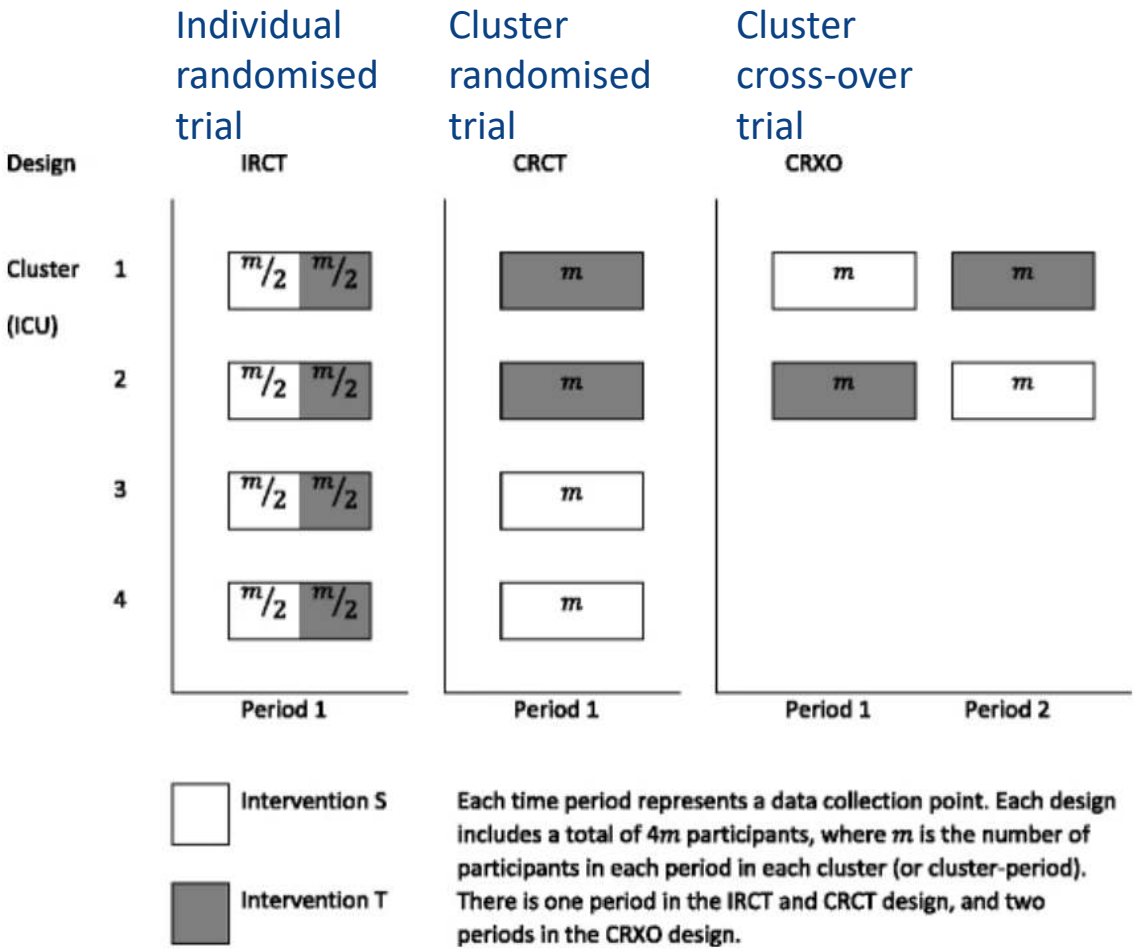
Population	Individuals living in villages in Eastern Myanmar
Intervention	3-day supervised course of antimalarial treatment administered monthly for 3 months to all individuals living in village
Comparator	No antimalarial treatment
Outcome	Prevalence of malaria
Time	Cross-sectional surveys performed every 3 months for 24 months
(study design)	??

Cluster cross-over trials

No CONSORT extension currently available

See proposal for reporting items
Arnup S et al. Trials 2016

Cluster cross-over trials



Clusters are exposed to both control and treatment conditions

Two "cluster-periods"

Cross-sectional design – each cluster-period consists of different individuals

Cohort design – each cluster-period consists of the same individuals

Arnup S et al. Trials 2017

Cluster cross-over trials:
Incorporation of clustering into sample size

Unit of randomisation: cluster,

Note, randomly allocating each cluster to a sequence (e.g. AB or BA for interventions A and B)

Unit of outcome measure: individual

Key information required:-

- Within-cluster between-period correlation: measures how similar patient outcomes are within the same cluster, but in different periods
- Within-cluster within-period correlation: measures how similar patient outcomes are within a given cluster-period

Cluster cross-over trials

Pros

- Within-cluster comparison - variability of outcome for treatment effect reduced because less variability within- than between-clusters
- Fewer clusters needed than a parallel cluster randomised trial *(only if within-cluster between-period correlation > 0)*

Cons

Carry over effect of the intervention (*design assumes minimal carry over effect*)

Clusters drop out after 1st intervention and don't receive 2nd intervention

Generally, only suitable for

- participants with conditions or diseases that are chronic or relatively stable *(for cohort designs)*
- short-term outcomes that have low variation between cluster-periods
- For cohort designs, interventions with short term impact, so washout period is feasible
- For cross-sectional designs, interventions at cluster level that can be crossed-over easily

Quiz??

An investigator comes to you with a research question they would like to investigate, see the PICOT below.

Would a cluster cross-over trial be appropriate/feasible?

Yes or No

Population	Patients attending ICUs in Australia
Intervention	New procedural intervention to improve discharge planning
Comparator	Standard procedures at ICU
Outcome	Length of stay in ICU
Time	Recorded for all patients attending ICU over a 6 month period
(study design)	??

Stepped wedge cluster randomised trials

CONSORT 2010 statement: extension to stepped wedge cluster randomised trials
Hemming K et. al. BMJ 2018

Key features of statement

- Rationale for adopting a stepped wedge design instead of a parallel design for cluster randomized trial
- Schematic representation of the design – number of steps, number of observations per cluster period
- Incorporation of clustering and adjustment for time in sample size estimation and analysis

Stepped wedge cluster randomised trials

- All clusters receive the intervention
- Clusters are randomised to one of several different sequences which set the time of crossover from control to intervention period
- More clusters are exposed to the intervention towards the end of the study
- The timing of the implementation of the intervention is indicated by steps, with the number of steps and step lengths determined by the design

Cluster (village)	Baseline	Period 1	Period 2	Period 3	Period 4	Period 5	Period 6	Period 7	Period 8	Period 9	Period 10	Period 11	Period 12
Cluster 1													
Cluster 2													
Cluster 3													
Cluster 4													
Cluster 5													
Cluster 6													
Cluster 7													
Cluster 8													
Cluster 9													
Cluster 10													
Cluster 11													
Cluster 12													

Post-Intervention measurement

Control measurement

Stepped wedge cluster randomised trials

Rationale

- All clusters receiving the intervention increases the social appeal of the study
- Evaluates how interventions would work in real-world settings
- Allows an evaluation of an intervention within the context of a routine roll-out

Things to consider when choosing this design

- The effect of the intervention might be confounded with any underlying temporal trend
- Sample size calculations and analysis must make allowance for both the clustered nature of the design and temporal confounding
- Is there any possibility that the effect of the intervention might vary over the duration of the study

Stepped wedge cluster randomised trials

Pros

- Evaluates interventions that are delivered at cluster level
- Avoids contamination of the intervention to individuals *not yet* randomised to the intervention
- Increases feasibility and participant compliance for some interventions
- All clusters receive the intervention, evaluates how an intervention would be implemented in practice

Cons

- Temporal confounding of intervention effect
- Intervention may change over time
- Sample size needs to be increased by design effect (intracluster correlations for within-clusters at a single time point & across time points, & number of individuals per cluster)
- Large number of clusters required
- Trial may take a long time to complete because number of steps

Quiz??

An investigator comes to you with a research question they would like to investigate, see the PICOT below.

Would a stepped wedge cluster randomised trial be appropriate/feasible?

Yes or No

Population	Individuals attending general practices in metropolitan areas of Sydney and Melbourne with high levels of refugee resettlement
Intervention	Training of general practice teams to optimise routines of refugee care
Comparator	Standard care by general practice teams
Outcome	Proportion of patients from refugee backgrounds with documented health assessments
Time	Outcome data collected over 12 months
(study design)	??

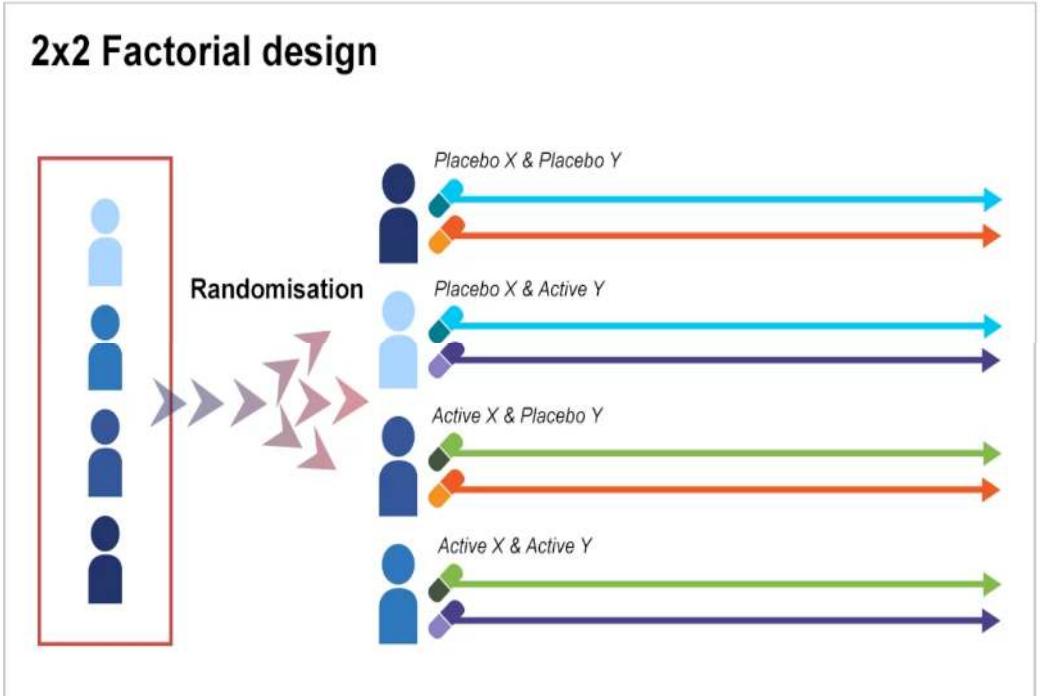
Factorial designs

RAFT: Reporting Factorial Trials – Extension to CONSORT guidelines in progress

Both A & B	**A Only**
B Only	**Neither A nor B**

Factorial designs – simplest form (2x2)

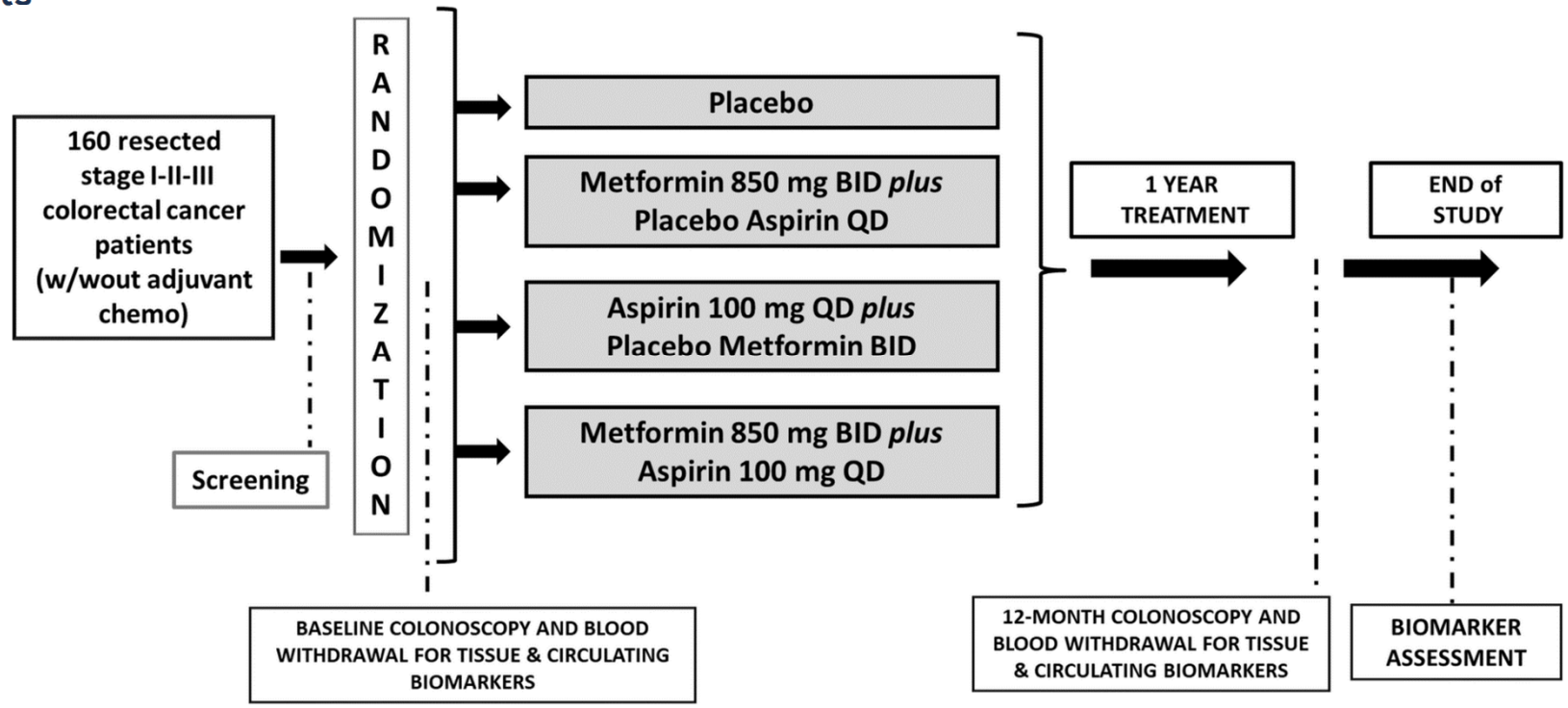
- Parallel individual RCT
- Participants are randomised to 4 arms
    - intervention A & intervention B
    - intervention A & placebo B
    - intervention B & placebo A
    - placebo A & placebo B



Factorial designs

Study protocol | Open Access | Published: 04 December 2018

The ASAMET trial: a randomized, phase II, double-blind, placebo-controlled, multicenter, 2 × 2 factorial biomarker study of tertiary prevention with low-dose aspirin and metformin in stage I-III colorectal cancer patients



Factorial designs: *Rationale*

If the two interventions work independently (i.e. no interaction is expected) then:-

- Factorial designs offer an efficient design for evaluating multiple interventions
- Two trials for about the price of one
- 50% of participants receiving each intervention in a 2x2 factorial design

Strong assumption of no interaction, is it met?

If an interaction is expected:-

- Factorial design is the only way to assess it
- But requires substantial sample sizes

Montgomery et al Design, analysis and presentation of factorial randomised controlled trials. BMC Med Res Methodol. 2003; 3:26

Factorial designs

Pros

- Efficient design and less costly for evaluating multiple interventions, if there is no interaction between the effect of the interventions on the outcome

Cons

- Much larger sample size required if there is an interaction between the effect of the interventions on the outcome
- Limited generalisibility
- Increased complexity when interaction of the interventions effect are present

Quiz??

An investigator comes to you with a research question they would like to investigate, see the PICOT below.

Would a factorial 2x2 randomised trial be appropriate/feasible?

Yes or No

Population	Newly diagnosed hypertensive adults
Intervention	(a) computerised utility assessment interview about high blood pressure (b) information leaflet about high blood pressure
Comparator	No intervention
Outcome	Total score on the Decisional Conflict Scale
Time	Follow-up questionnaire collected immediately after intervention before returning to GP
(study design)	??

Summary

Cross-over trials

- Suitable for short term outcomes, interventions that have no carry over effect, feasible and ethical to randomise participants to receive an intervention A and intervention B/control
- Sample size and statistical analysis needs to account for within-participant variation

Cluster randomised trials

- Suitable for interventions delivered at cluster level or interventions where there could be contamination in clusters if delivered at individual level
- Sample size and statistical analysis needs to account for clustering

Cluster cross-over trials

- Suitable for short term outcomes, interventions that have no carry over effect, feasible and ethical to randomise clusters of participants to receive an intervention A and intervention b/control
- Sample size and statistical analysis needs to account for clustering (between and within-clusters, and between periods)

Summary

Stepped wedge cluster randomized trials

- Suitable for short term outcomes, interventions that are going to be rolled out and not expected to vary over the study time period
- Sample size and statistical analysis needs to account for clustering and temporal variation

Factorial designs

- Efficient design for assessing multiple interventions that work independently

References

- Arnup S et al. The quality of reporting in cluster randomised crossover trials: proposal for reporting items and an assessment of reporting quality. *Trials 2016*
- Arnup S et al. Understanding the cluster randomised crossover design: a graphical illustration of the components of variation and a sample size tutorial. *Trials 2017*
- Campbell MK et al. CONSORT 2010 statement: extension to cluster randomised trials. *BMJ 2012*
- Dwan K et al. CONSORT 2010 statement: extension to randomised crossover trials. *BMJ 2019*
- Hemming K et al. Reporting of stepped wedge cluster randomised trials: extension of the CONSORT 2010 statement with explanation and elaboration. *BMJ 2018*
- Montgomery AA et al. Design, analysis and presentation of factorial randomised controlled trials. *BMC Med Res Methodol. 2003; 3:26*

What is HeSANDA

- **Health Studies Australian National Data Asset (HeSANDA)** is a national program that makes health and medical research data easier to find
- Facilitates access, sharing and reuse of research data
- 9 nodes representing over 70 research organisations around Australia have been working together through HeSANDA to develop **Health Data Australia**
- **Health Data Australia** is a searchable online catalogue where you register clinical trial metadata, where secondary researchers can browse and submit an access request to be considered for secondary use of trial data.

MACH Melbourne Academic Centre for Health

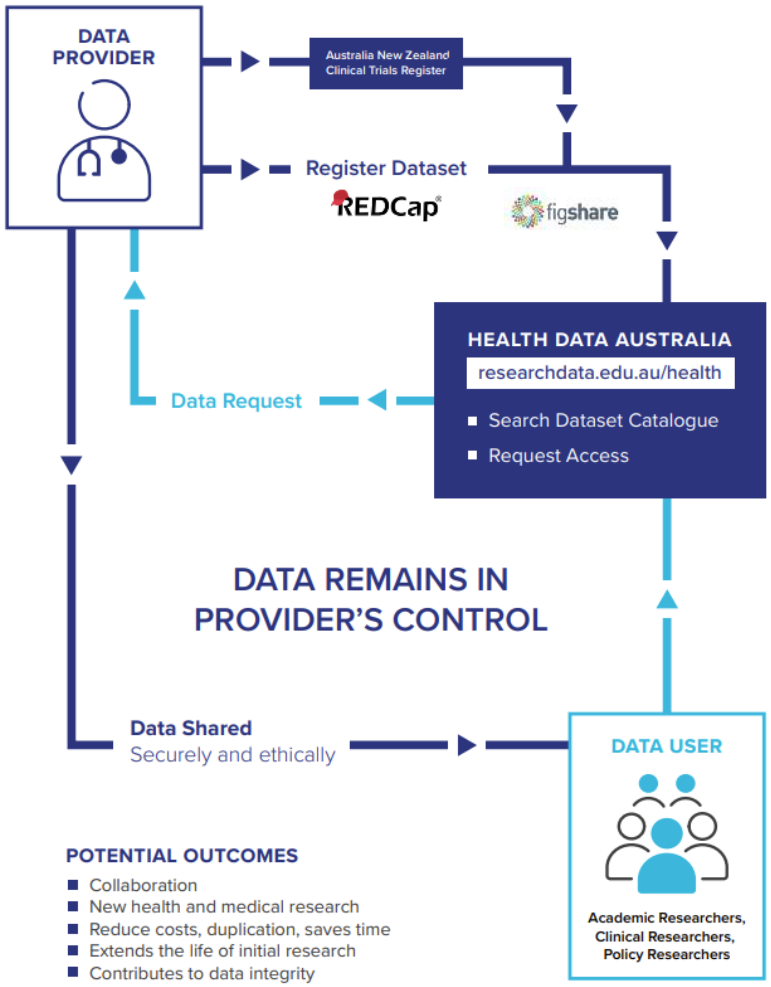
Australian Research Data Commons

NCRIS

How it works

1. Ensure your trial registration is up to date in ANZCTR and ‘Section 11 – Data Sharing’ indicates your willingness to share data

2. Complete MACH node REDCap form with non-sensitive clinical trial descriptive metadata

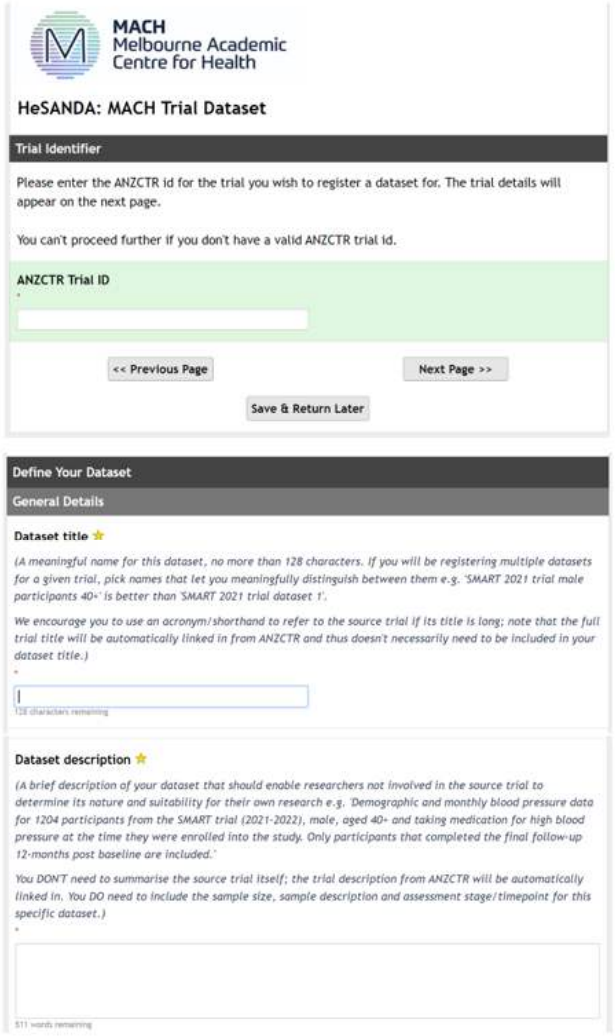


MACH Melbourne Academic Centre for Health

Australian Research Data Commons

NCRIS

MACH REDCap metadata registration form – 5-10mins maximum



MACH
Melbourne Academic Centre for Health

HeSANDA: MACH Trial Dataset

Trial Identifier

Please enter the ANZCTR id for the trial you wish to register a dataset for. The trial details will appear on the next page.

You can't proceed further if you don't have a valid ANZCTR trial id.

ANZCTR Trial ID *

<< Previous Page | Next Page >> | Save & Return Later

Define Your Dataset

General Details

Dataset title ★

(A meaningful name for this dataset, no more than 128 characters. If you will be registering multiple datasets for a given trial, pick names that let you meaningfully distinguish between them e.g. 'SMART 2021 trial male participants 40+' is better than 'SMART 2021 trial dataset 1'.

We encourage you to use an acronym/shorthand to refer to the source trial if its title is long; note that the full trial title will be automatically linked in from ANZCTR and thus doesn't necessarily need to be included in your dataset title.) *

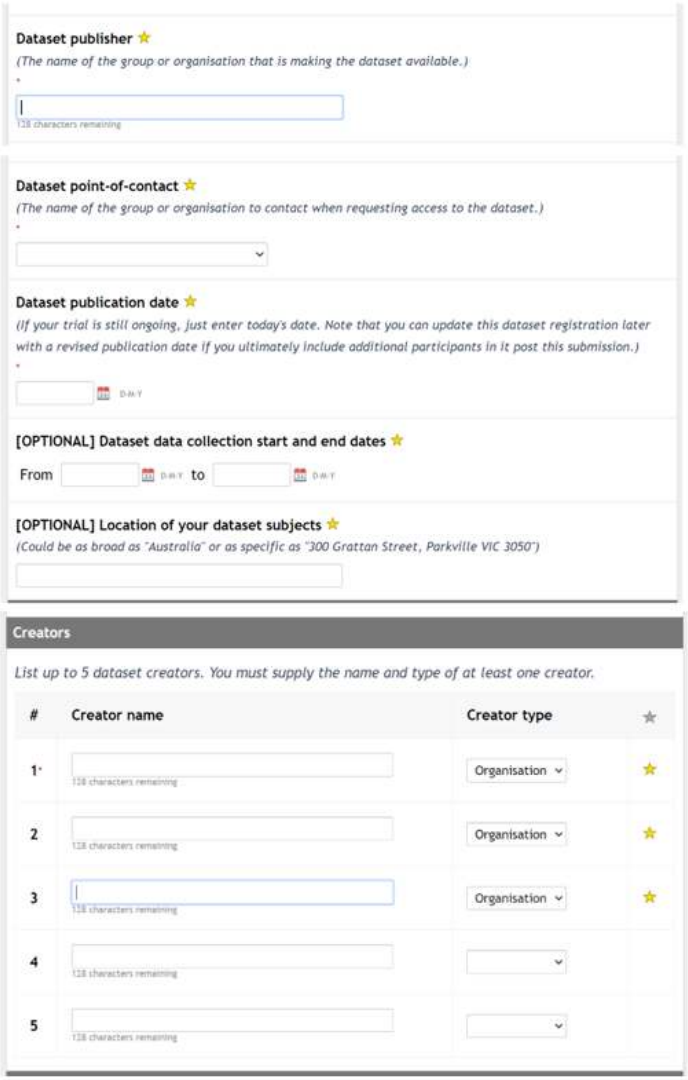
128 characters remaining

Dataset description ★

(A brief description of your dataset that should enable researchers not involved in the source trial to determine its nature and suitability for their own research e.g. 'Demographic and monthly blood pressure data for 1204 participants from the SMART trial (2021-2022), male, aged 40+ and taking medication for high blood pressure at the time they were enrolled into the study. Only participants that completed the final follow-up 12-months post baseline are included.'

You DON'T need to summarise the source trial itself; the trial description from ANZCTR will be automatically linked in. You DO need to include the sample size, sample description and assessment stage/timepoint for this specific dataset.) *

511 words remaining



Dataset publisher ★

(The name of the group or organisation that is making the dataset available.) *

128 characters remaining

Dataset point-of-contact ★

(The name of the group or organisation to contact when requesting access to the dataset.) *

Dataset publication date ★

(If your trial is still ongoing, just enter today's date. Note that you can update this dataset registration later with a revised publication date if you ultimately include additional participants in it post this submission.) *

D-M-Y

[OPTIONAL] Dataset data collection start and end dates ★

From D-M-Y to D-M-Y

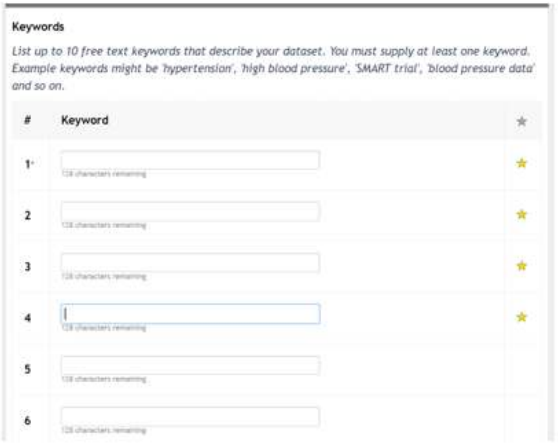
[OPTIONAL] Location of your dataset subjects ★

(Could be as broad as "Australia" or as specific as "300 Grattan Street, Parkville VIC 3050")

Creators

List up to 5 dataset creators. You must supply the name and type of at least one creator.

#	Creator name	Creator type	★
1*	128 characters remaining	Organisation	★
2	128 characters remaining	Organisation	★
3	128 characters remaining	Organisation	★
4	128 characters remaining		
5	128 characters remaining		



Keywords

List up to 10 free text keywords that describe your dataset. You must supply at least one keyword. Example keywords might be 'hypertension', 'high blood pressure', 'SMART trial', 'blood pressure data' and so on.

#	Keyword	★
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2	128 characters remaining	★
3	128 characters remaining	★
4	128 characters remaining	★
5	128 characters remaining	
6	128 characters remaining	

NCRIS
National Research Infrastructure for Australia
An Australian Government Initiative

Health Data Australia Portal

https://researchdata.edu.au/health

Contact MACH HeSANDA Node

hesanda-mach@unimelb.edu.au

Add your trial dataset to HDA

https://redcap.link/mach-hesanda

MISCH Hub

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