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How, when and why to engage with biostatisticians when undertaking randomised controlled trials

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Housekeeping

- Please keep your microphone switched off during the presentation.
- You are welcome to leave your video on or off as you prefer.
- If you have any questions, please feel free to enter them in the chat box. We will review them throughout the presentation and at the end.

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Faculty of Medicine, Dentistry and Health Sciences

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Statistical support at the end…

Can you fix the stats?

Can you make the reviewers happy?

Can you salvage the project?

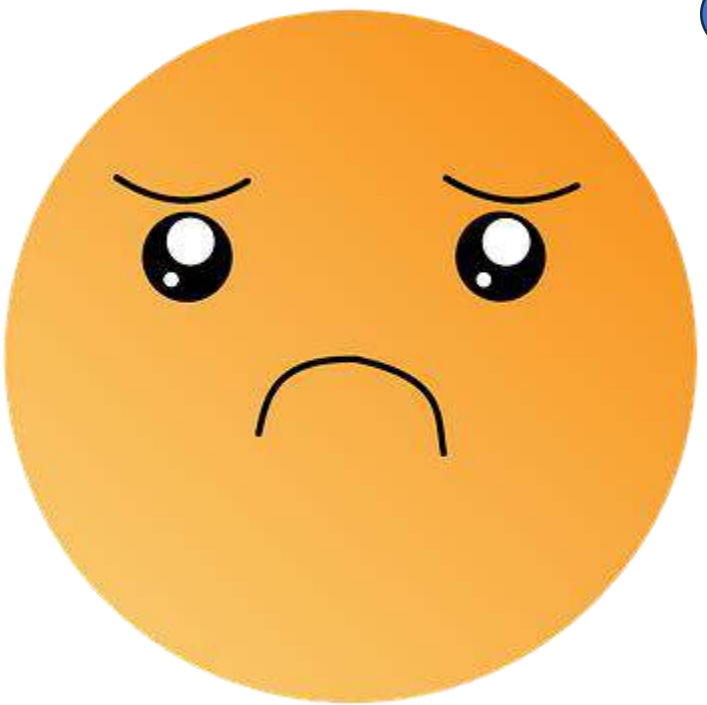
"You can't fix by analysis what you bungled by design"

Light R, Singer J, Willett J (1990), By Design

…can lead to disappointment…

You don't have enough participants

Your study design isn't right



You have not collected the data you need

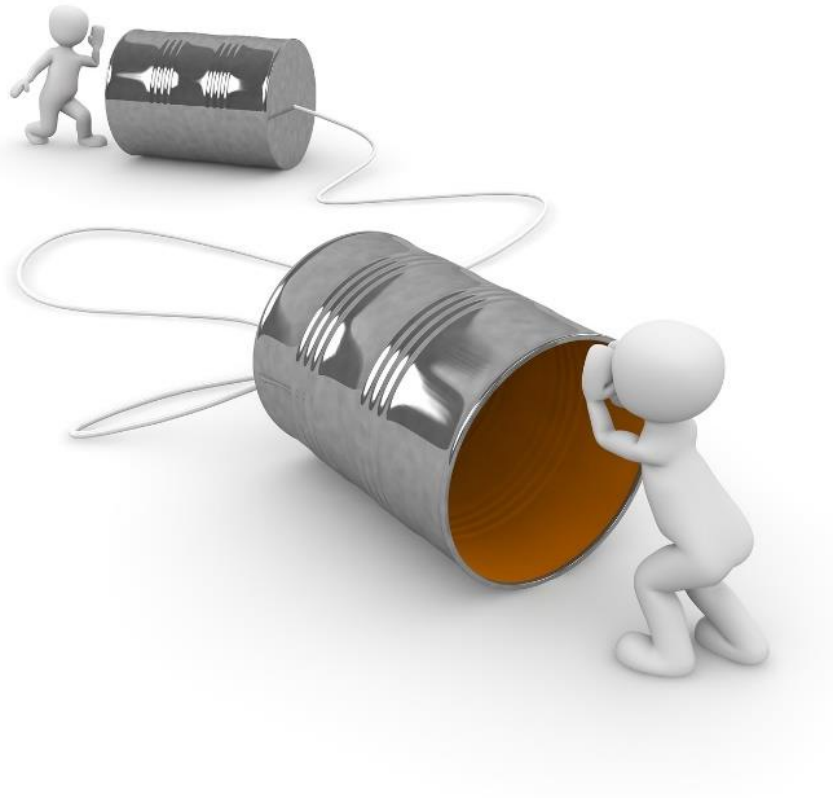
You have too much missing data

…so engage early with a biostatistician.

- It is critical to involve a biostatistician as early as possible when developing your randomised controlled trial (RCT)
- We can identify the appropriate design and help determine the number of participants needed
- Sometimes after the grant and protocol development, collaborators disappear - this can lead to problems

Communication during an RCT

- Need to ensure biostatisticians are consulted at appropriate times during a trial
- The aim of this presentation is to describe the stages involved in an RCT and how and why a biostatistician should be involved



RCT – Key stages

STUDY DESIGN → PROTOCOL DEVELOPMENT → SURVEY DEVELOPMENT → DATABASE DEVELOPMENT → RANDOMISATION → DATA CHECKING → DSMB → STATISTICAL ANALYSIS PLAN → ANALYSIS AND REPORTING

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RCT – Key stages

STUDY DESIGN

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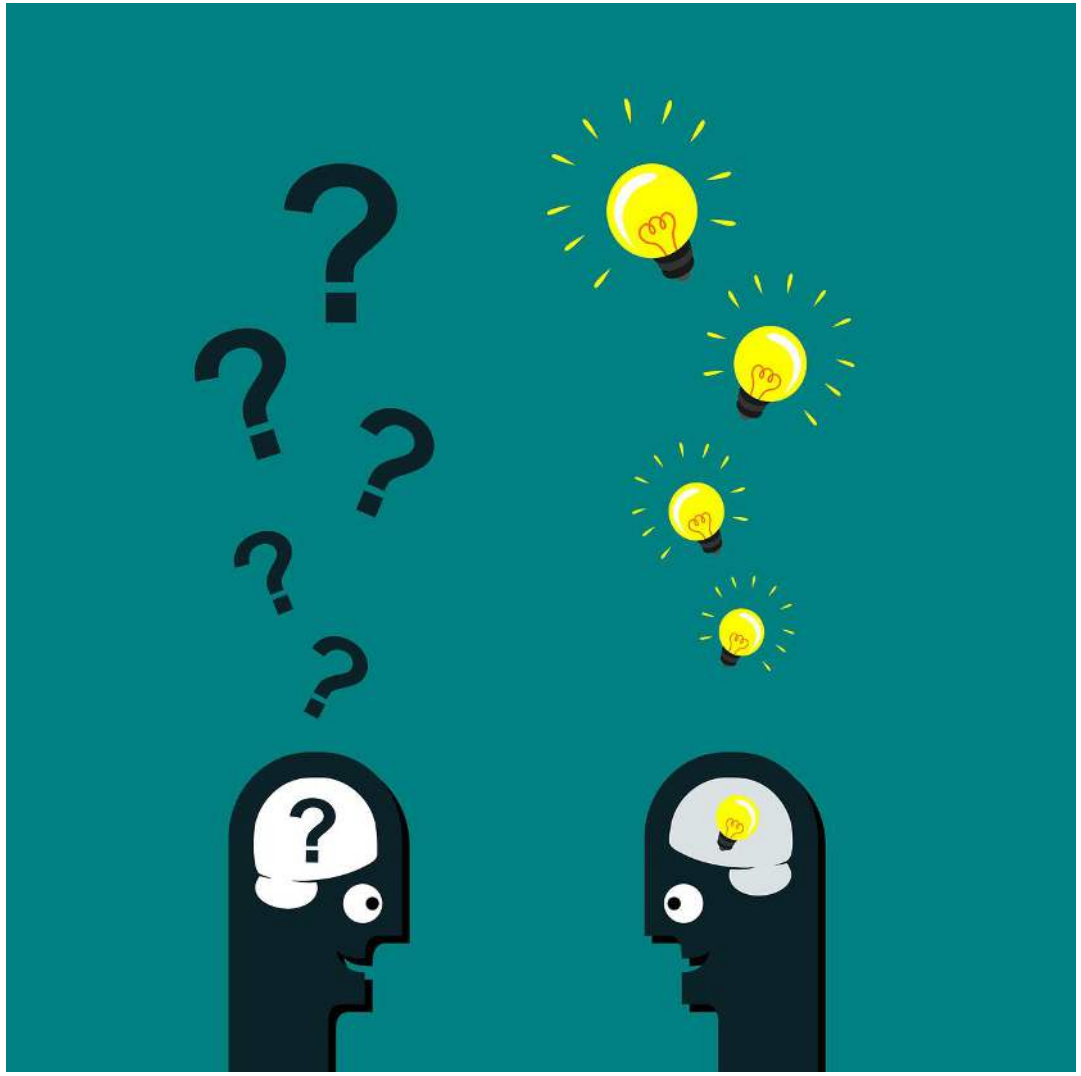
Study design

- Biostatisticians should be consulted as early as possible in the initial planning

- We help with:

i) Refining the research question (including defining the estimand of interest)
ii) Study design (e.g., parallel-arm, cluster)
iii) End-points/outcome(s)
iv) Comparator arms
v) Population
vi) Blinding
vii) Randomisation
viii) Data collection
ix) Sample size



RCT – Key stages

STUDY DESIGN → PROTOCOL DEVELOPMENT

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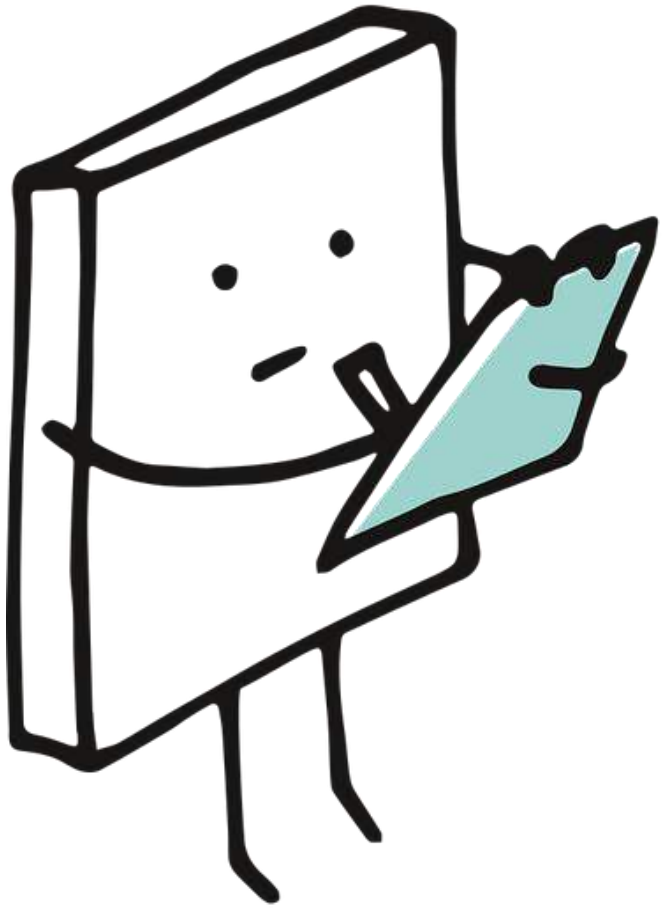
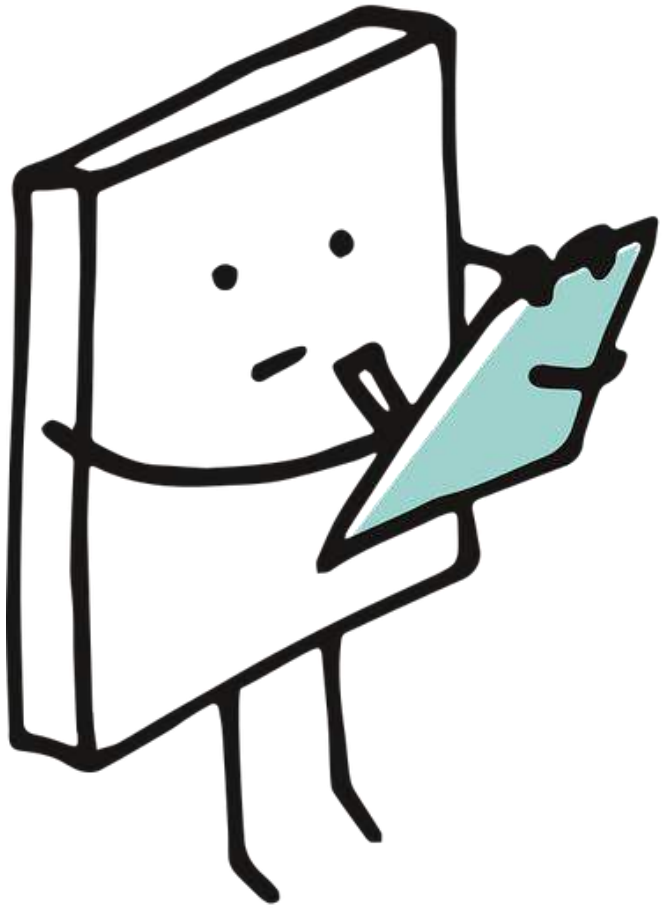
Protocol development



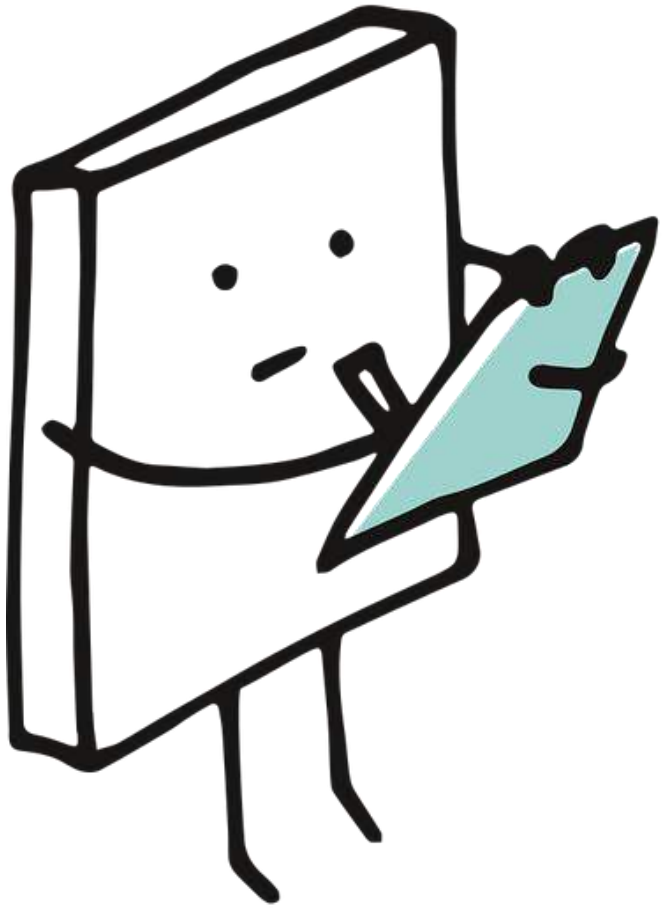
- The trial biostatistician(s) **must** be involved in the protocol review
- Biostatisticians help ensure the research question is clear
- This includes defining the estimand of interest
- Biostatisticians typically write the **sample size** and **analysis** sections

Protocol development



- Reviews do not only focus on the statistics sections (blinding, randomisation, sample size, analysis)
- Full reviews are required to check consistency (e.g., primary outcomes clear and remain the same, sample size does not change, etc.)
- MISCH has a **checklist** for reviewing protocols to ensure the key elements are present

Protocol development



- The trial biostatistician(s) are commonly **named on the trial protocol**
- They should review the protocol prior to submission to ethics
- Note that a protocol review for a straightforward trial can take **half a day to a full day** for the hands-on biostatistician
- A **further 2-3 hours** may be required for the oversight biostatistician
- **Allow more time for complex studies!** Non-typical study designs require more statistical time.

Protocol development

- The biostatistician **must** be informed of any changes to the protocol
- A change may not seem like it will impact the statistics, but many changes do
- **Check with the study biostatistician(s) if the change will impact the study!**
- The biostatistician **must** be provided with the most up-to-date version of the protocol
- Changes to the protocol may result in ethics amendments and/or changes to the trial registry

Protocol development

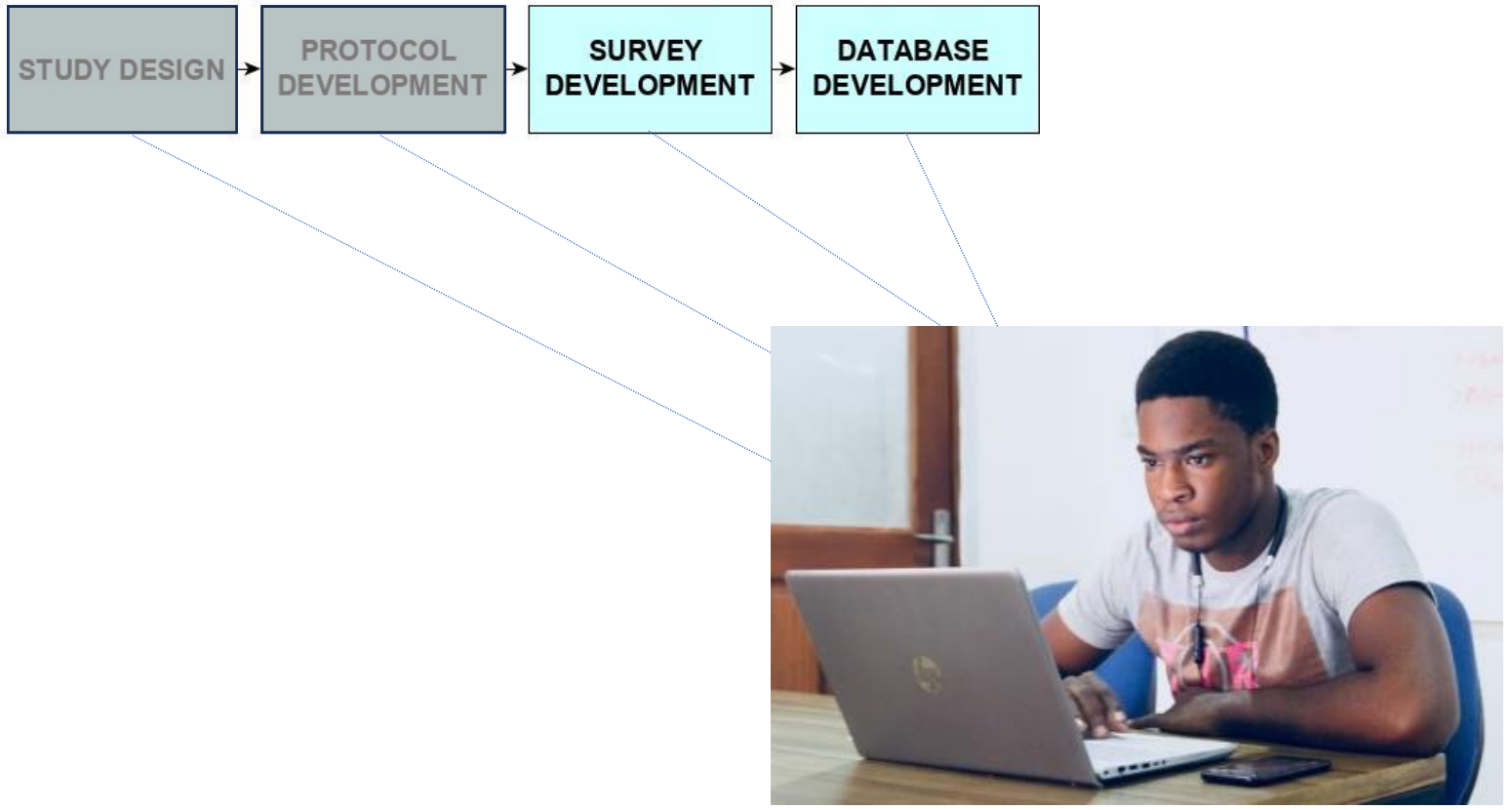
- Commonly, protocols for RCTs are published in peer reviewed journals
- The trial biostatistician(s) should be included as **co-author(s)** on the protocol paper
- The biostatistician will **thoroughly review** the protocol paper; this takes time!
- Be sure to allocate sufficient time for biostatistical review – 24-hour turnaround times typically don’t work for us!

Trial registration

- Trials should be registered with the Australian New Zealand Clinical Trials Registry: https://www.anzctr.org.au/

- Trial biostatisticians should be consulted on what should be included in the trial registration, particularly the sample size and analysis sections

RCT – Key stages



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Survey/CRF and database development

- Survey/questionnaire/case report form (CRF) and database development are critical for RCTs
- The trial biostatistician(s) are sometimes left out of this process
- This can lead to problems at the analysis stage

Survey/CRF and database development

We help develop surveys/questionnaires or case report forms (CRFs) and the database to:

- Check the outcome(s) data are collected appropriately
- Ensure other necessary data are captured (e.g., demographic data, data prognostic of the outcome)
- Check question wording and order makes sense
- Avoid open-ended questions when quantitative data are needed
- Help avoid missing data
- Check questionnaires/database able to collect data at all time-points needed

Survey/CRF and database development

- Trial biostatisticians will:

i) Cross-check paper surveys or CRFs with the database to ensure no inconsistencies

ii) Test the database to ensure branching logic works (if needed)

iii) Advise on approaches to avoid impossible values in the database (e.g., setting plausible ranges for variables like age)

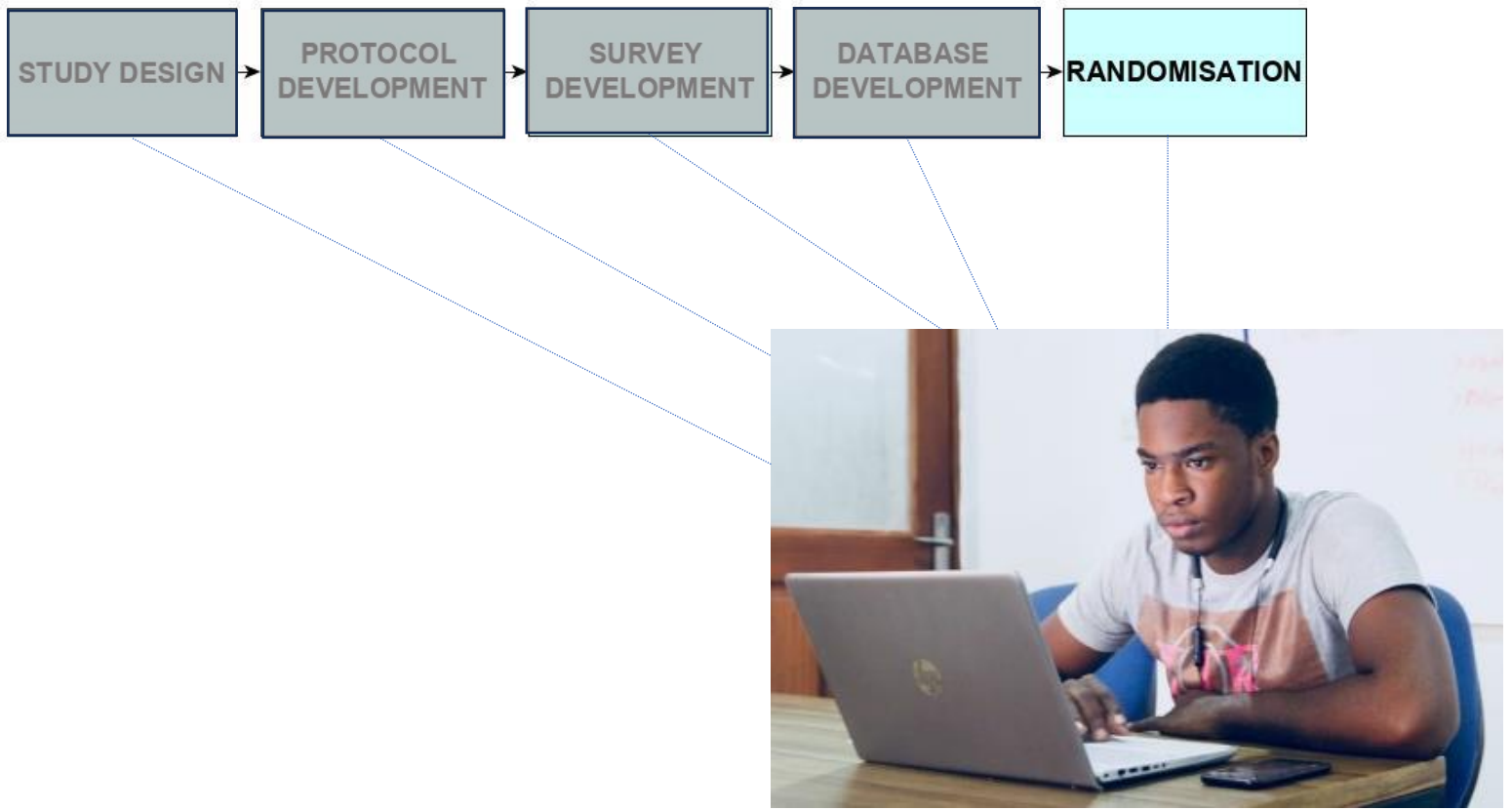
iv) Examine test data entered in the database to check it is fit for purpose

- MISCH has a **checklist** for reviewing surveys and databases

Survey and database development

- Do not underestimate the time it can take to develop surveys/CRFs and databases
- MISCH biostatisticians commonly request at least **two months** to help develop surveys and databases for larger trials
- The trial biostatistician undertakes the detailed assessment – **this can take at least one full day**
- An oversight biostatistician will provide an additional assessment to identify any key issues
- Survey and database development can take a few iterations to reach the final product

RCT – Key stages



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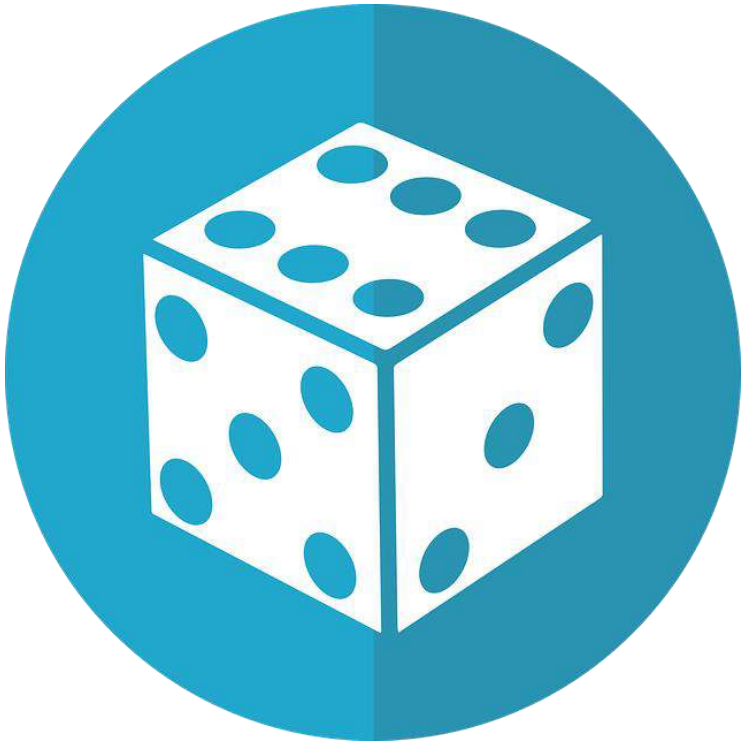
Randomisation

- Randomisation requires **at least two biostatisticians**
- The **trial biostatistician** will develop the code for the randomisation list
- This is commonly checked by the oversight biostatistician
- An **external/independent biostatistician** is required to run the code to create the list, ensuring the study and oversight biostatisticians remain blinded to treatment allocation
- The list will be sent by the independent biostatistician to the data manager on the study who does not need to be blind to treatment allocation

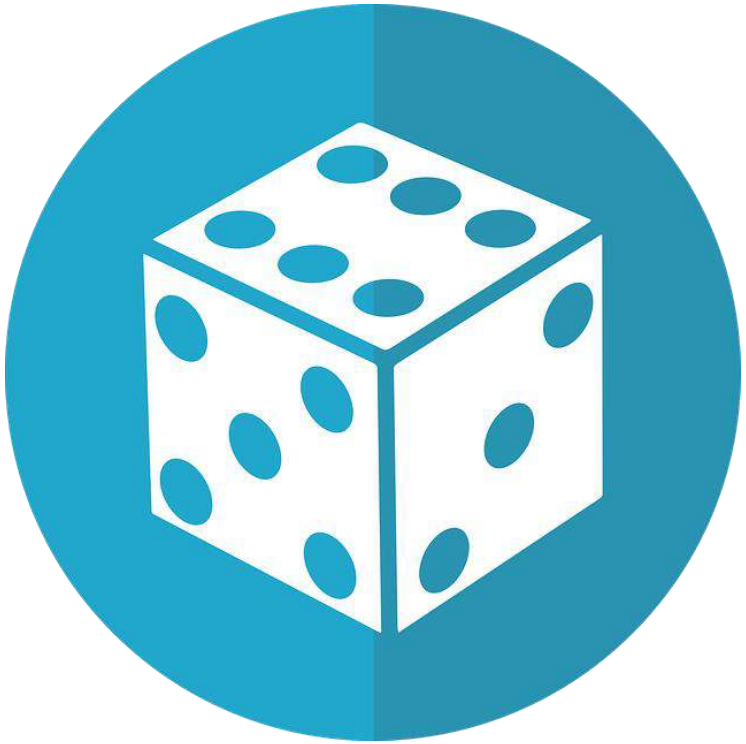


Randomisation

- In MISCH, we need **1-2 months notice** to create a randomisation list

- We need to identify someone within the team to act as independent biostatistician who will never be involved in the trial analysis

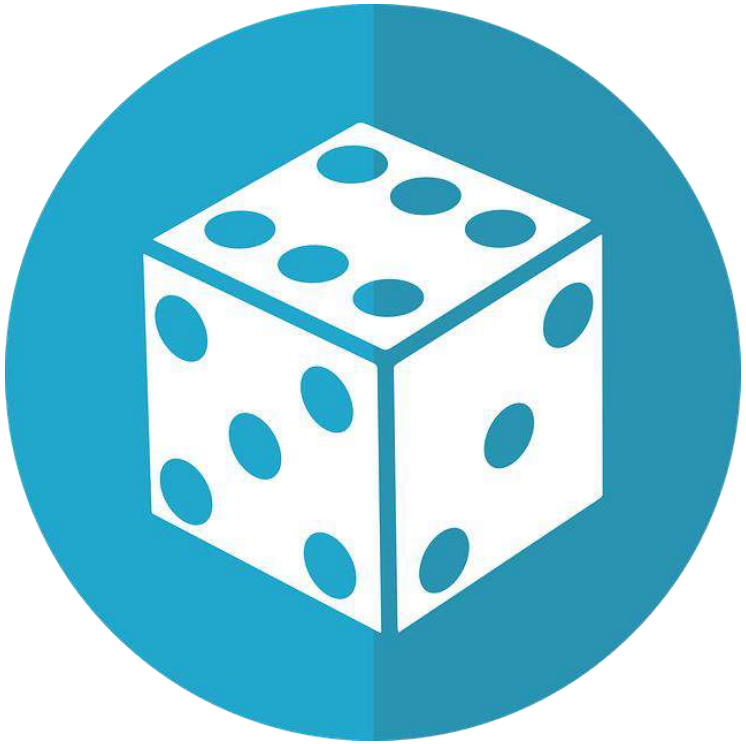
- The trial biostatistician will extract relevant information from the protocol about randomisation to create the code (e.g., 1:1 ratio, stratification variables, sample size)



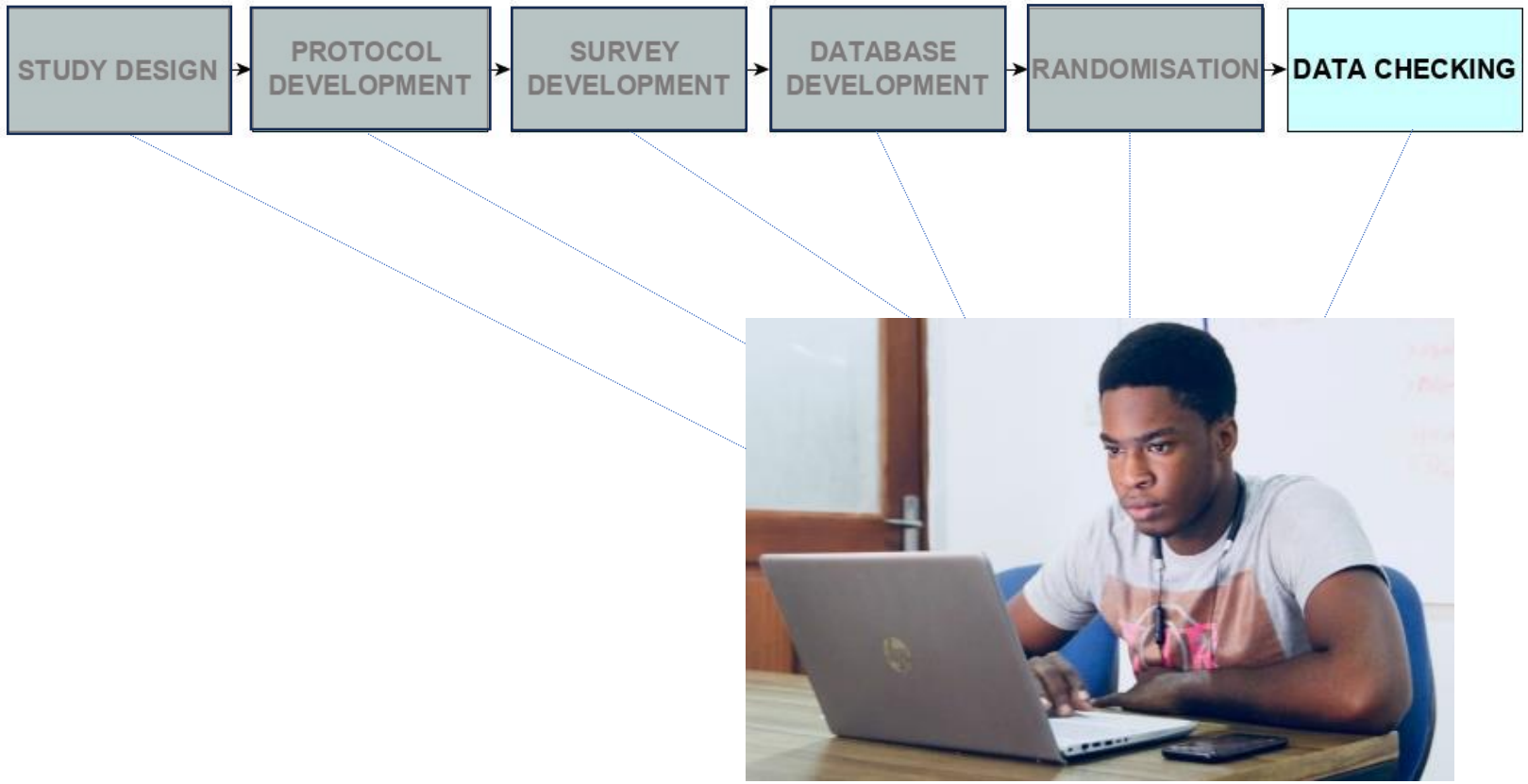
Randomisation

- We recommend factoring time into the database development to trial the randomisation list before the study goes live

- This means two randomisation lists may be created: the test list and the final list



RCT – Key stages



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Data checking

- It is important to check the data **while the trial is in progress**
- This can identify important issues which could be rectified early
- Sometimes this is conducted as part of a **data safety monitoring board** (DSMB) report but it may be part of **study tracking**
- It is important to ensure the trial biostatistician(s) and investigators who should be blinded remain blinded to treatment allocation during these checks

Data checking

- Some trials develop **data validation/management plans** to support the protocol and statistical analysis plan
- The trial biostatistician(s) can **support the development** of a data validation or management plan
- These plans are not the sole responsibility of the trial biostatistician(s) but are developed by the **chief investigator**, **project manager** and **data manager** (where possible)
- These can be very useful to ensure the data are cleaned appropriately prior to analysis

Data checking

- Key checks:

i) Number recruited (tracking as planned)

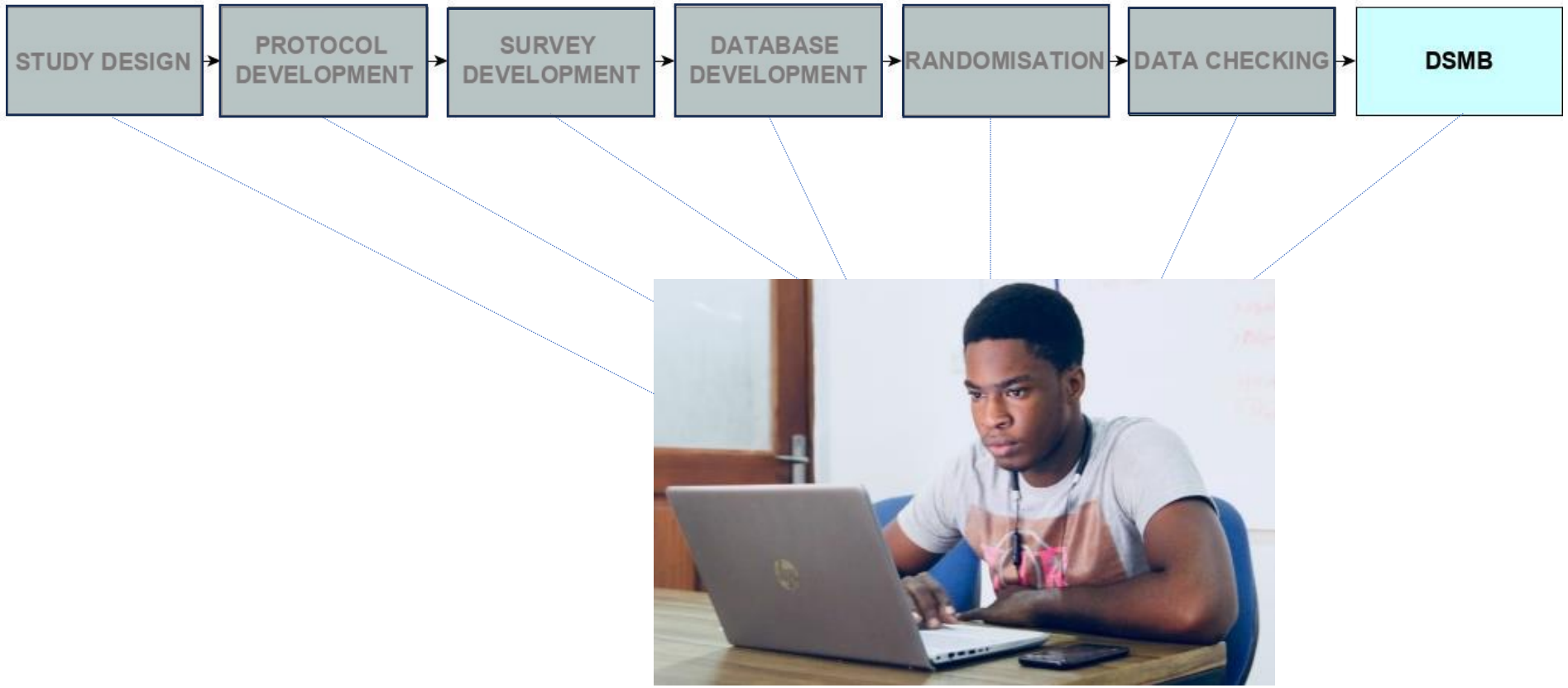
ii) Loss to follow-up

iii) Baseline data complete

iv) Outcome data – values are valid, no/limited missing data

v) Adverse events

RCT – Key stages



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DSMB

- Data Safety Monitoring Boards may be required, particularly if your study has risks of serious adverse events

- DSMBs need at least **three biostatisticians**

- These are:

i) the trial biostatistician(s),

ii) an independent biostatistician,

iii) the DSMB biostatistician

DSMB

- The **trial biostatistician(s)** will create template reports and code for the open and closed DSMB meetings
- These templates and reports will be created in collaboration with the lead investigator and database manager
- The **trial biostatistician** will complete the report for the **open meeting**

DSMB

- The open report will be sent to the person responsible for coordinating the DSMB meeting
- The person coordinating the DSMB meeting should be someone involved in the trial who does not need to be blind to treatment allocation
- An **oversight biostatistician** may be involved to review the open report and code

DSMB

- The **independent biostatistician** will create the **closed report** using the code and template provided
- This is the report with data presented by treatment group
- The database manager will provide information about the randomisation to the independent biostatistician to create this report

DSMB

- The **independent biostatistician** will cross-check the closed report against the open report to check for any inconsistencies

- They will send the report to the person responsible for the DSMB meeting

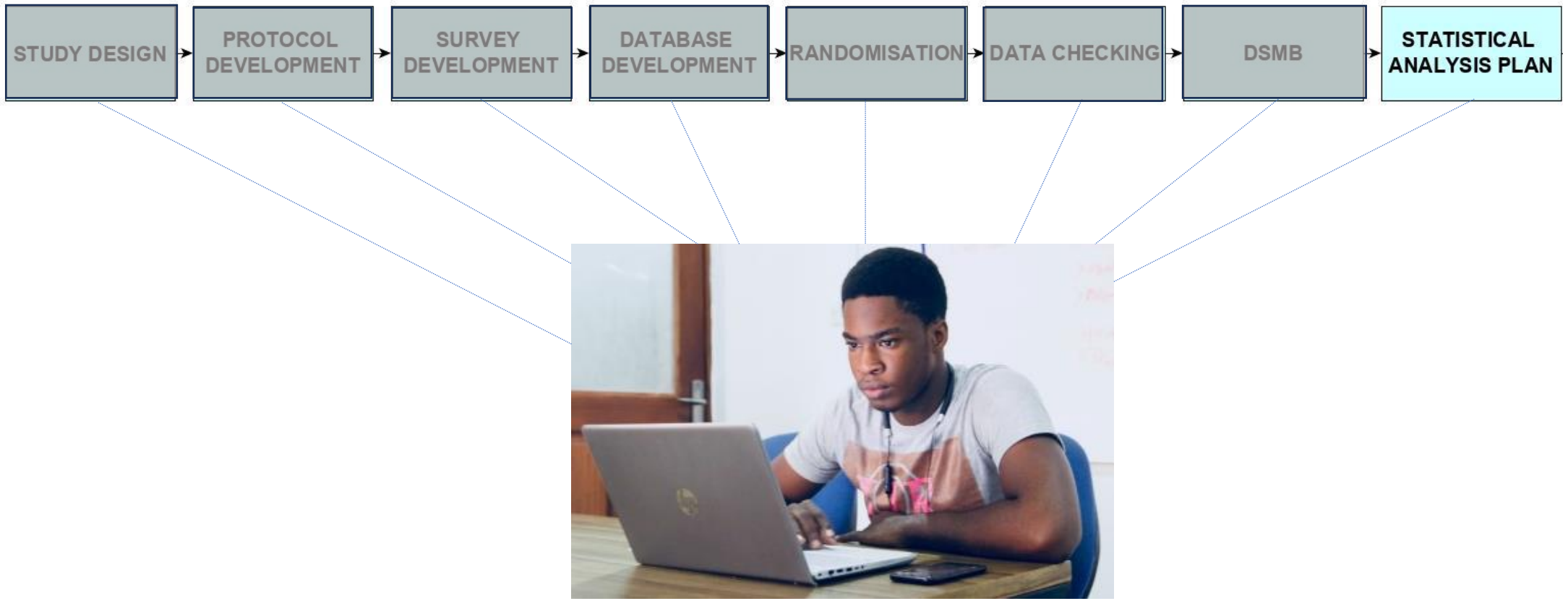
DSMB

- The open and closed reports will be sent to the DSMB members who are independent of the trial
- DSMBs should contain a biostatistician who will review the reports with statistical issues in mind
- The trial biostatistician (and oversight biostatistician, if needed) will only attend the meeting about the open report
- The independent biostatistician who prepared the closed report may attend the meeting about the closed report, in addition to the open meeting
- The DSMB biostatistician will attend both meetings

DSMB

- DSMB reports can take time to prepare, particularly the first report when the trial biostatistician is becoming familiar with the data
- MISCH biostatisticians typically request a notice period of **2-3 months** prior to a DSMB meeting to prepare a report
- Although these can be time consuming, DSMBs do offer the trial biostatistician hands-on work with the data to be analysed in the trial

RCT – Key stages



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Statistical analysis plan

- RCTs require a detailed statistical analysis plan to be developed and finalised prior to unblinding
- MISCH biostatisticians typically begin preparing SAPs **at least 6 months** before the final observation for the final participant is anticipated
- The SAP should be consistent with the protocol so the biostatistician must have the most up-to-date version of the protocol

Statistical analysis plan

- Some trials choose to publish the statistical analysis plan separately in a peer-reviewed journal
- Journals like *Trials* publish statistical analysis plans
- The main trial biostatistician will typically be lead author on this publication, with the oversight biostatistician as senior author
- If planning on publishing the statistical analysis plan in a journal, the plan should be developed and final **12-18 months prior to database lock**

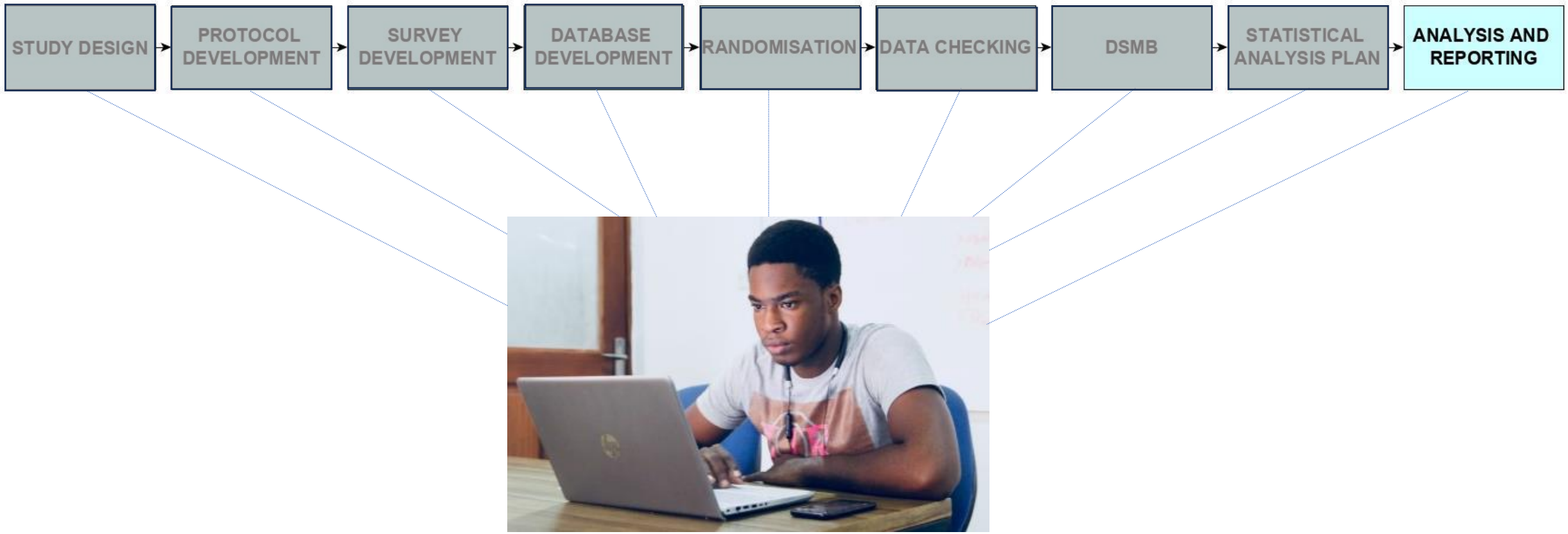
Statistical analysis plan

- All analyses outlined in the trial SAP should be included in the main trial paper
- The detailed SAP, or a link to the detailed SAP, should be published with the main trial paper
- All analyses should be agreed on before the trial unblinding
- The final SAP should be signed by the trial biostatistician(s) and lead investigator

Statistical analysis plan

- Prior to finalising the SAP, it is common to have:
  - A blinded data review meeting
  - A database lock meeting
- These meetings provide an opportunity to discuss key data issues prior to unblinding
- These meetings typically only include the lead investigator, trial biostatisticians, data manager and/or project manager

RCT – Key stages



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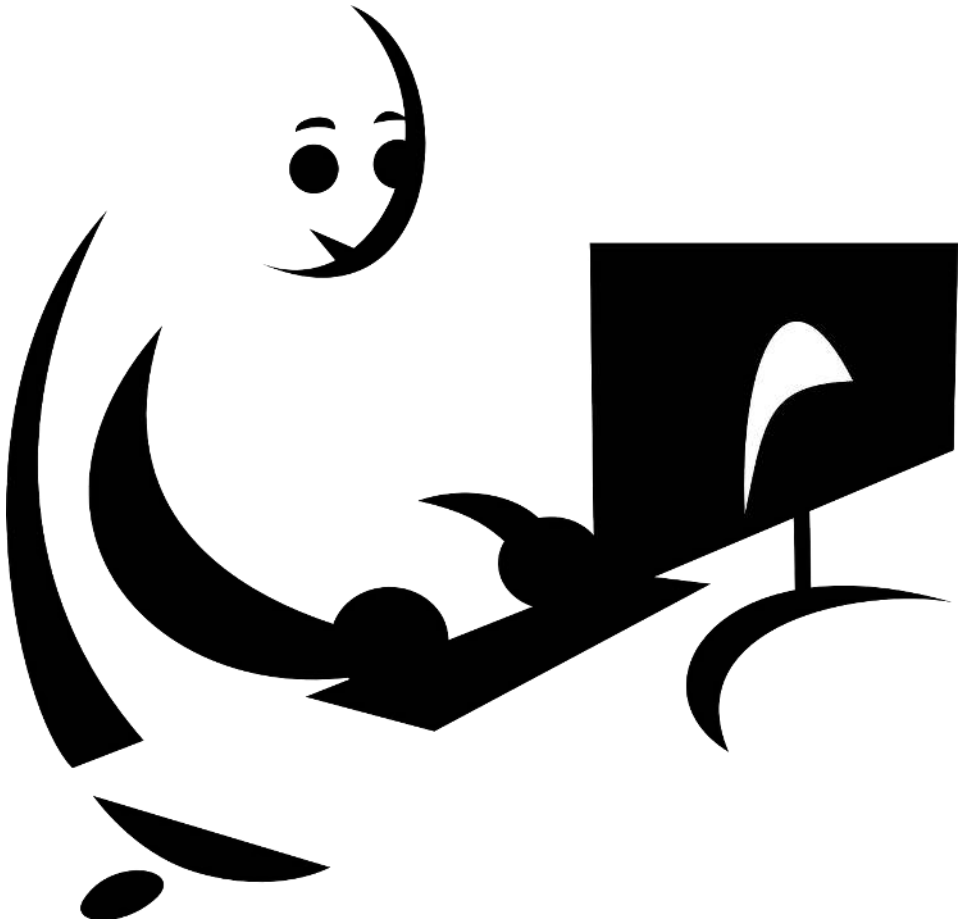
Analysis and reporting

- Where possible, cleaned data should be provided to MISCH biostatisticians
- Biostatisticians should advise on data cleaning and preparation



Analysis and reporting

- While developing the SAP, the trial biostatistician will have developed template tables for the report/publication
- This will help with the analysis but inevitably challenges arise when analysing data
- MISCH biostatisticians typically request **3-6 months** to analyse and report findings from RCTs
- It is preferable to have much of this time **prior to database lock** rather than following database lock to avoid post-hoc changes to the statistical analysis plan

Analysis and reporting

- Investigators should work closely with the trial biostatistician(s) when writing a paper on the trial findings
- Trial biostatistician(s) provide a key role in writing up the trial results for publication
- The statistical analysis plan should include template tables and figures for the paper
- Trial biostatistician(s) commonly assist in drafting the methods and results sections
- Trial biostatisticians will review the whole paper and provide input on interpretation, strengths and limitations in the discussion
- It is common to include the trial biostatistician to be **second or third author** on papers reporting trial findings, in acknowledgement of their biostatistical leadership

Communication is key!

- If biostatisticians are not kept in the loop about changes to the trial, things can go very wrong!

- From our trial experience, this has included:
  - The primary outcome changing after the trial has begun recruitment
  - Questionnaires have been removed from the study after the trial has commenced
  - Changes to usual care have occurred during the trial which have not been documented

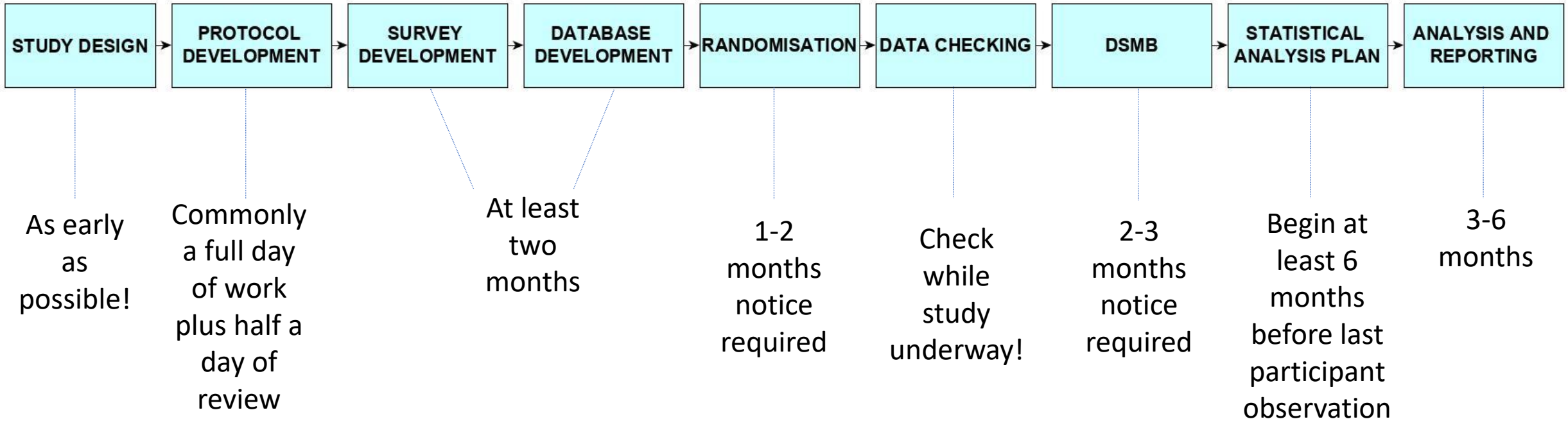
Benefits of working closely

- Careful planning at the beginning avoids mistakes at the end of the trial
- Taking time to develop questionnaires and databases means data should be usable and missing/incorrect data will be minimised
- If your biostatistician is familiar with your database at the start, this will help at the analysis stage

What we didn’t cover

- Interim analyses
- Complex trials with many analyses (e.g., adaptive trials)
- Observational studies (e.g., prediction modelling, mediation analysis, reliability studies)
- Systematic reviews (with or without meta-analysis)
- These all involve careful planning and timely communication

RCT – MISCH Biostatistics timelines



MISCH collaborations

- Timely access to research methods and services is essential to building top-tier clinical research

- An appropriately qualified biostatistician can inform study design, conduct, analysis and reporting

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Thank you!

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