Metro North Hospital and Health Service *Putting people first*

11 August 2020 | Live via Teams

Writing your Clinical Research Protocol

Tuesday, 02 March 2021

Facilitated by Professor Janet Davies, Assistant Director Research
MNHHS Office of Research
MNHHS-Research@health.qld.gov.au

Queensland Government

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Agenda

Part 1 Introduction (15 min) Professor Janet Davies

Part 2 Overview Clinical Research Education Resources (5 min)

Natasha Roberts
Specialist Nurse, CCS
Metro North HHS Clinician
Research Fellow since 2021

Associate Professor Jayesh Dhanani
Staff Specialist, ICU RBWH
Metro North HHS Clinician Research
Fellow since 2020

Part 3 Questions (10 min)

What's next & session close

Please do not mention any confidential details of patients or research.

Teams Virtual session,

Facilitated by Prof Janet Davies, MNHHS Office of Research MNHHS-Research@health.qld.gov.au

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What is Research?

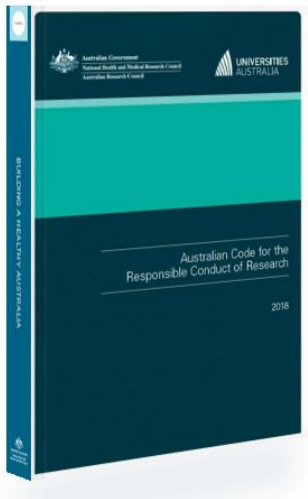
"Research will provide our patients with the best access in Australia To novel diagnostics, innovative therapeutics and advanced health services"

Definition:
Original investigation to **gain knowledge**, understanding and insight.

The concept of research is broad;
- **creation of new knowledge,** and/or
- **use of existing knowledge in a new and creative way,** to generate
- new concepts, methodologies, inventions and understandings.

This could include synthesis and analysis of previous research to the extent that it is new and creative.
MNHHS Research Policy (004365 effective Feb 2020)

Australian Code for the Responsible Conduct of Research (the Code)

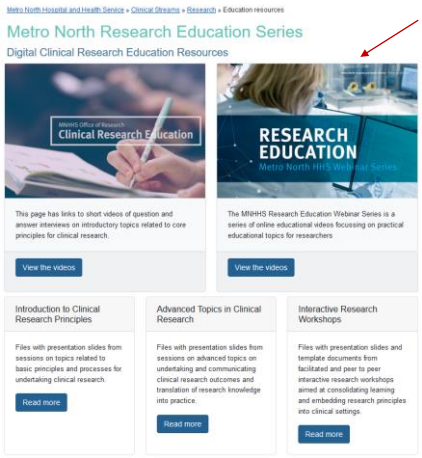


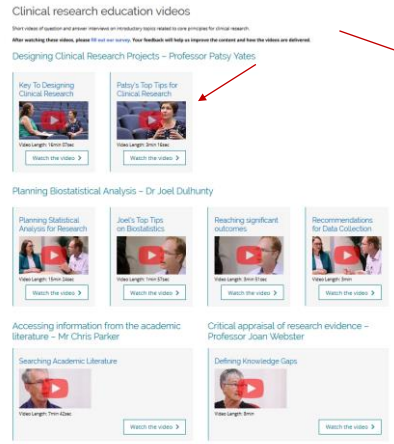
The following hallmark principles of **responsible research conduct** provide the **framework for integrity** in the **design, conduct and communication** of research:

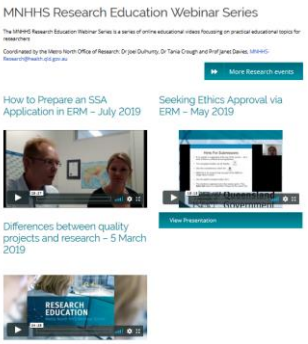
- **Honesty** in the development, undertaking and reporting of research
- **Rigour** in conducting high-quality research
- **Transparency** in declaring conflicts of interest and reporting research methodologies and findings
- **Fairness** in the treatment of others
- **Respect** for research participants, the wider community, animals and the environment
- **Recognition** of Aboriginal and Torres Strait Islander peoples or communities significantly involved in or affected by research
- **Accountability** for the conduct of research
- **Promotion** of responsible conduct in the research community

Clinical research education resources and tools

https://metronorth.health.qld.gov.au/research
https://qheps.health.qld.gov.au/metronorth/research/education-resources







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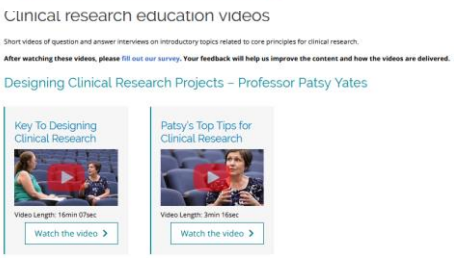
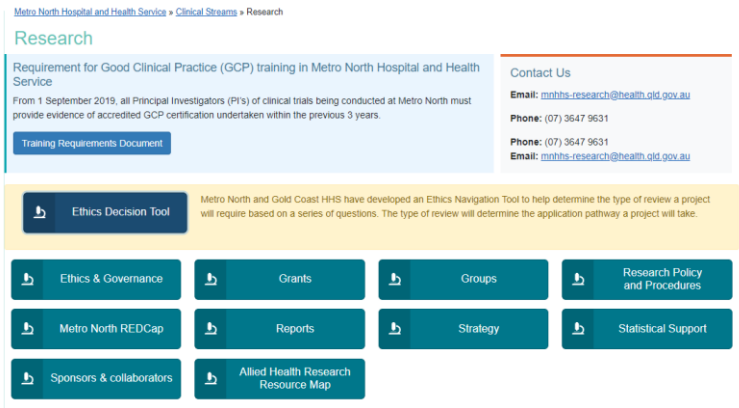
Education resources relevant to research design





https://metronorth.health.qld.gov.au/research/clinical-research-education-videos

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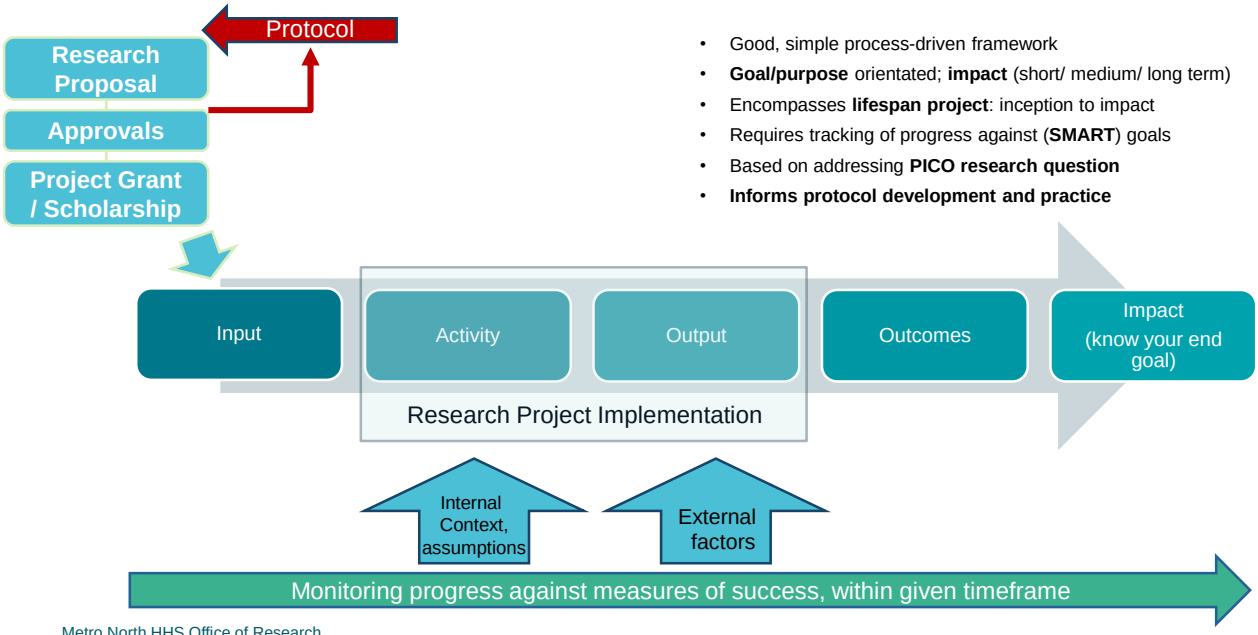
Program logic model for clinical research



- Good, simple process-driven framework
- **Goal/purpose** orientated; **impact** (short/ medium/ long term)
- Encompasses **lifespan project**: inception to impact
- Requires tracking of progress against (**SMART**) goals
- Based on addressing **PICO research question**
- **Informs protocol development and practice**

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https://qheps.health.qld.gov.au/__data/assets/pdf_file/0032/2448365/rpm.pdf

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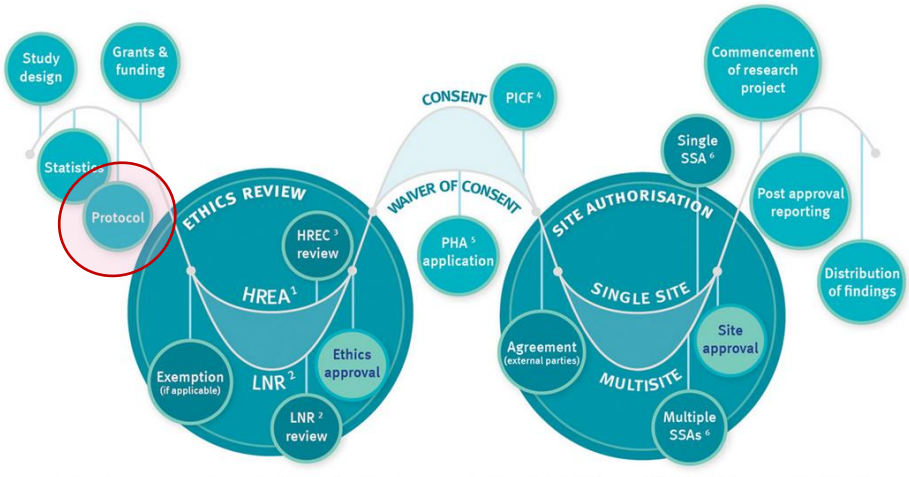
https://metronorth.health.qld.gov.au/research/ethics-and-governance

Research process

Key steps in the research approval process are shown in the diagram below.



Note: the above diagram does not represent proporational time speant in each stage. [1] Human Research Ethics Application (HREA), [2] Low or negligible risk (LNR), [3] Human Research Ethics Committee (HREC), [4] Participant Information and Consent Form (PICF) - requires ethics review, [5] Public Health Act (PHA), [6] Site Specific Assessment (SSA).

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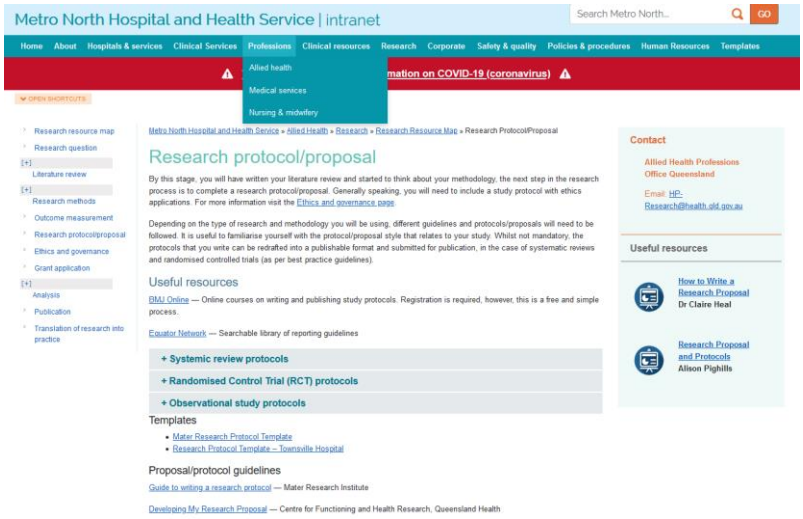
https://qheps.health.qld.gov.au/metronorth/allied-health/research/research-resource-map/protocol-proposal



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Natasha Roberts

Specialist Nurse, CCS

Metro North HHS Clinician Research Fellow since 2021

- Prostate Cancer Specialist Nurse at RBWH
- has a PhD and leads research studies both locally and nationally
- has worked in both ICU and Medical Oncology Clinical Trials
- has expertise in qualitative research, mixed methods and clinical trials
- has received over $325,000 in grant funding
- is the first recipient of a MNHHS Clinician Research Fellowship from within the nursing and midwifery stream
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How to write a clinical research protocol

Natasha Roberts
Prostate Cancer Specialist Nurse
Metro North Fellow

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Contents

1. Introduction
2. What is a study protocol?
3. Where to start
4. Different types of a study protocols
5. A worked example of a qualitative study

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What is a study protocol?

- "A clinical study protocol is a document that describes the study objectives, design, methods, assessment types, collection schedules, and statistical considerations for analysing data. The protocol outlines the steps for protecting subjects and obtaining quality data"

(WHO, 2021)

Ref: https://www.who.int/groups/research-ethics-review-committee/recommended-format-for-a-research-protocol/

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Where to start:

- What is your research question?
- What are your methods?
- Who is your team?
- Where the study is being done?
- Who is the sponsor?

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Clinical Trials Protocols (quantitative outcomes)

- If interventional, is there clinical equipoise with intervention?
- Is participant enrolment and data collection feasible?
- How will data be collected and stored? Electronically?
- Randomised? How?
- Defining primary, secondary and tertiary outcomes
- Statistical power and sample size justification
- Statistical analysis plan (strong biostatistical support)
- Data safety monitoring committee
- Trial registration
- Funding?

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Examples of types of outcomes

Table 3. Primary, secondary and tertiary study outcomes

	Outcomes
Primary outcome	▪ All-cause mortality within 90 days after randomisation
Secondary outcomes	▪ Clinical cure at Day 14 after randomisation
	▪ New acquisition, colonisation or infection with an MRO or *Clostridium difficile* diarrhoea up to 14 days after randomisation
	▪ All-cause ICU mortality
	▪ All-cause hospital mortality
Tertiary outcomes	▪ ICU length of stay
	▪ Hospital length of stay
	▪ Duration of mechanical ventilation in ICU up to 90 days after randomisation
	▪ Duration of renal replacement therapy up to 90 days after randomisation

A protocol for a phase 3 multicentre randomised controlled trial of continuous versus intermittent β-lactam antibiotic infusion in critically ill patients with sepsis: BLING III

Jeffrey Lipman, Stephen J Brett, Jan J De Waele, Menino O Cotta, Joshua S Davis, Simon Finfer, Parisa Glass, Serena Knowles, Shay McGuinness, John Myburgh, David L Paterson, Sandra Peake, Dorrilyn Rajbhandari, Andrew Rhodes, Jason A Roberts, Charudatt Shirwadkar, Therese Starr, Colman Taylor, Laurent Billot and Joel M Dulhunty

Trial registration: ClinicalTrials.gov Registry (NCT03213990).

Crit Care Resusc 2019; 21 (1): 63-68

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A worked example of a qualitative study

What is it like to be in a clinical trial?

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This protocol included:

- **Synopsis**
- Background
- Study aims
- Theoretical approach
- Study design
- Study population and setting
- Study procedures
- Data collection
- Data analysis
- Safety considerations
- Dissemination of findings
- Ethical and regulatory considerations
- References

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Synopsis:

The purpose of this study is to qualitatively explore and describe the experience of participating in a clinical trial, across the clinical trial trajectory with emphasis on pre-trial, during treatment, and after the trial intervention finishes.

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This protocol included:

- Synopsis
- **Background**
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Background:

- How the study was “born”?
- Who is the research team?
- Why it needs to be done?
- What does the literature say?

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This protocol included:

- Synopsis
- Background
- **Study aims**
- Theoretical approach
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Study aims

- The global aim of this study is to describe the experience of participating in a clinical trial. The specific aims are to explore:

1. Participant recall and experience of the stages of clinical trial participation including: learning about the trial, deciding to take part, the informed consent process, being randomised, being in the trial, study assessments, when treatment finishes, follow-up, and hearing the results.

2.Clinical trial participants' perception of how their cancer treatment experience differed due to taking part in a clinical trial;

3.Identify strategies to improve the experience of taking part in a clinical trial.

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This protocol included:

- Synopsis
- Background
- Study aims
- **Theoretical approach**
- Study design
- Study population and setting
- Study procedures
- Data collection
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- References

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You need a theoretical foundation to your work

- "knowledge is of two kinds. We know a subject ourselves, or we know where we can find information upon it" Albert Einstein

- Thank you to Ian Grahame from KT Canada, and Gill Harvey from University of Adelaide for allowing me to use these slides

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Anyone afflicted by FAS? Framework Averse Syndrome?

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A few warning signs and symptoms:

- Eye rolling
- Sighing
- Involuntary utterances
- OMG
- HML
- JKMN
- Hyperventilating
- Fainting

Data apparently shows that it is less common among nurses and women…

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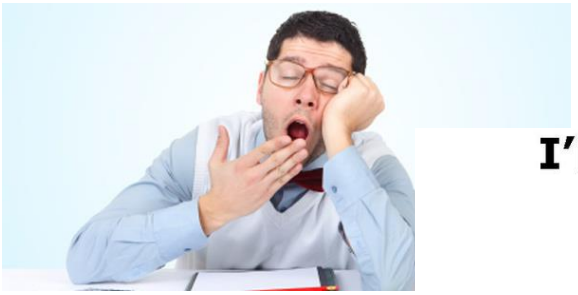
"There is nothing as practical as a good theory"



I'm so excited.

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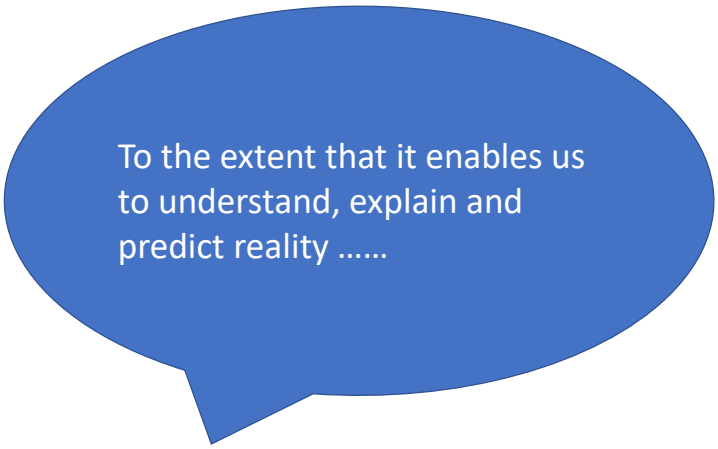
"there is nothing as practical as a good theory"



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This protocol included:

- Synopsis
- Background
- Study aims
- Theoretical approach
- Study design
- Study population and setting
- Study procedures
- **Data collection**
- Data analysis
- Safety considerations
- Dissemination of findings
- Ethical and regulatory considerations
- References

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Data collection

- Interview guide:
  - ➢What do you want to know
  - ➢What evidence is out there and how does it apply to this project?
  - ➢Apply theoretical constructs
  - ➢What questions/observations will get you the information you need

Eg, Patients see a clinical trial in sections

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- Each interview will be audio recorded and transcribed verbatim. The qualitative interview transcripts will be coded and subjected to thematic analysis using a framework approach. This involves simultaneous data collection and analysis, together with systematic efforts to check and refine developing categories of data. In addition to the research questions formulated at the outset, it is anticipated others may emerge during the period of data collection.

- Methodological rigor will be ensured through: i) interviewer memos; ii) transcript review; iii) verbal debriefing; iv) member-checking; v) multiple and cross-coding; and, vi) iterative revision of the interview guide.

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This protocol included:

- Synopsis
- Background
- Study aims
- Theoretical approach
- Study design
- Study population and setting
- Study procedures
- Data collection
- **Data analysis**
- Safety considerations
- Dissemination of findings
- Ethical and regulatory considerations
- References

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Data Analysis

The qualitative data will be analysed using a method of thematic analysis developed by Ritchie and Spencer (2002), the framework approach. Gale, Heath, Cameron, Rashid, and Redwood (2013) adapted the framework approach to health research and detailed seven steps in the procedure. These steps will be implemented as follows:

- Transcribing –The interviews will be transcribed by a professional transcription service and checked against the recordings by the researcher.
- Familiarising with the data – for immersion in the data, the researcher reads and re-reads the interview transcripts and any contextual notes taken during the interviews.
- Coding – passages or lines in the transcripts will be labelled to reflect the key substantive things, values or beliefs contained.
- Developing a working analytical framework – after three transcripts are coded, the researchers will discuss the set of codes identified from with initial transcripts coded, this forms the analytical framework
- Applying the analytical framework – remaining transcripts will be indexed according to the analytical framework. The working framework will be edited throughout this process as new themes may be identified in subsequent transcripts.
- Charting data into a framework matrix – the data will be summarised into a matrix in Microsoft Excel, organised by cases and coded categories.

Basically you are looking at your data with rigour and from different perspectives

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This protocol included:

- Synopsis
- Background
- Study aims
- Theoretical approach
- Study design
- Study population and setting
- Study procedures
- Data collection
- Data analysis
- Safety considerations
- Dissemination of findings
- **Ethical and regulatory considerations**
- References

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ETHICAL, REGULATORY AND ADMINISTRATIVE ISSUES
(the references are a bit out of date because the protocol is a couple of years old)

The study will be performed in accordance with the "NHMRC National Statement on Ethical Conduct in Human Research" (Commonwealth of Australia, 2007- Updated May 2015) and the principles laid down by the 18th World Medical Assembly (Helsinki 1964) and amendments at subsequent World Medical Assemblies. No participants will be identified in any reports, and information identifying individual subjects will be removed from the data set prior to analysis.

10.1 **Human Research Ethics Committee (HREC) Oversight**

The study must be approved by the relevant HREC prior to commencing recruitment. Site specific approvals must be sent to each site Study Co-ordinator prior to commencing the study.

10.2 Informed Consent

Written information about the study will be provided to all participants, and written consent obtained after they have had time to review the information. Verbal consent will also be obtained prior to commencing interviews. The capacity to provide informed consent will be assessed by the clinical team at each site.

10.3 Confidentiality

Confidentiality of patients in the study will be strictly ensured. The Royal Brisbane and Women's Hospital will be the coordinating centre and will hold a separate secure database will be set-up containing contact details of those people agreeing to participate to ensure follow-up and any qualitative interviews are completed according to the protocol. Patient identification numbers will be generated here and used in a separate database containing the data generated by the study (this second database will not contain any other identifying information of participants).

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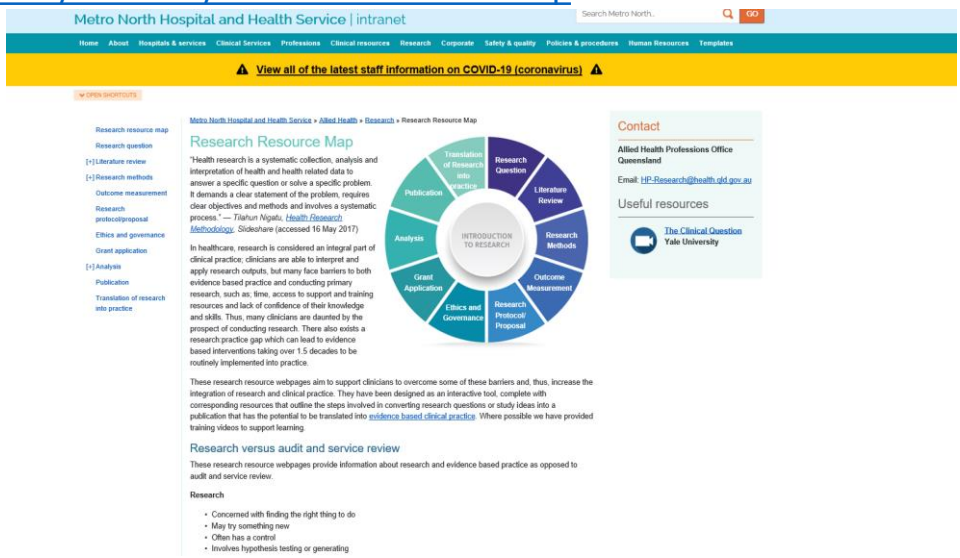
https://qheps.health.qld.gov.au/metronorth/allied-health/research/research-resource-map



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Associate Professor Jayesh Dhanani
Staff Specialist
Metro North HHS Clinician Research Fellow since 2020

- diverse fields; 'rationalisation of pathology tests in ICU', "blood sugar in ICU with clinical informatics integrated insulin infusion protocol'
- has supervised intensive care trainees and medical students toward their college projects
- has published 28 articles in peer-reviewed journals with RG score 26.1 and h-index 7
- has received over $1 million in grant funding
- current path breaking research: local pulmonary drug delivery with wide application for diverse patient groups

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Research Protocol example

Associate Professor Jayesh Dhanani
Metro North Clinician Research Fellow
Intensive Care Specialist-RBWH

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All science is the reduction of multiplicities to unities

Aldous Huxley

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Research Approach

- What's the problem?
- What's my proposed solution?
- What compelling experiments can I run to demonstrate the effectiveness of my solution?

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Can nebulization be used to deliver analgesia and sedation?

- Aerosol characterization
- Pharmacokinetics
- Safety
- Efficacy

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Has it been done before?

- Review of literature
- Types of study
- Methods- validation
- Drugs- safety
- Device for nebulization
- Results/outcomes

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Elements of Protocol development

- Discussed with the research co-ordinators
- Obtained a template from a 'successful' protocol
- Listed elements that I needed to complete
- Timeline to complete the first draft

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Study Drugs

- Fentanyl
- Morphine
- Ketamine
- Dexmedetomidine
- Clonidine
- Midazolam

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Doses

Same vs Different

Effect of different routes of administration on drug delivery

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Pharmacokinetics

- How much? Dose equivalency
- Compare with conventional- iv/oral/im/transcutaneous

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Patient population

Inclusion and Exclusion Criteria

- Mechanically ventilated
- Low oxygen requirement
- Not receiving CRRT
- Not allergic to drugs
- Receiving analgesia/sedation as per the treating clinician
- Likely to be ventilated for at least 2 days

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Patient Consenting

- Who does it?
- Telephone vs Direct
- Withdrawal from study

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Statistician

- Sample size estimation

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Data collection

- IT team
- RedCap
- Variables- made tables for the paper

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Table of contents looks like this

1 STATEMENT OF COMPLIANCE
2 PROTOCOL SIGNATURE PAGE
3 ADMINISTRATIVE INFORMATION
3.1 Chief Investigator
3.2 Co-Investigators
4 PROTOCOL SYNOPSIS
5 SUMMARY
6 INTRODUCTION
7 RESEARCH HYPOTHESES
8 STUDY OBJECTIVES
8.1 Primary Objectives
8.2 Secondary Objectives
9 STUDY DESIGN
9.1 Study Design
9.2 Setting
9.3 Patient recruitment
9.3.1 Inclusion criteria
9.3.2 Exclusion criteria
9.4 Study Drugs
9.5 Study Procedures
9.5.1 Intravenous drug administration
9.5.2 Nebulized drug administration
9.5.3 Blood Collection
9.5.4 Urine Collection
9.5.5 Sample handling and storage
9.5.6 Bioanalysis
9.5.7 Data collection on enrolment will include:
9.6 Number of Participants
9.7 Study Sites
9.8 Expected Duration of the Study
10 STATISTICAL AND PHARMACOMETRIC ANALYSIS PLAN
10.1 Power calculation and sample size
10.2 Pharmacometric analysis plan
11 ETHICS AND DISSEMINATION
11.1 Ethical principles
11.2 Independent Ethics Committee
11.3 Informed consent procedures
11.4 Participant Withdrawal
11.4.1 Reasons for withdrawal
11.4.2 Handling of withdrawals and losses to follow-up
12 SAFETY AND ETHICAL CONCERNS
12.1 Adverse events
12.2 Serious Adverse Events (SAE)
13 DATA COLLECTION AND MANAGEMENT
13.1 Data Confidentiality
13.2 Data Storage
13.3 Study Record Retention Error! Bookmark not defined.
14 OUTCOME AND SIGNIFICANCE
15 FUNDING
16 ADMINISTRATIVE ASPECT
16.1 Independent HREC approval
16.2 Amendments to the protocol
16.3 Protocol deviations
16.4 Participant reimbursement
17 USE OF DATA AND PUBLICATIONS POLICY.
18 REFERENCES

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Review and revision of draft

- Liaised with co-investigators and other collaborators
- Discussed with research co-ordinators
- Presented in the department research steering committee meeting
- Circulated amongst the department colleague clinicians

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Study title

- Acronym is a must
- Unique identifier
- PISA- A comparative study of **p**lasma pharmacokinetics of intravenous and **i**nhaled **s**edatives and **a**nalgesic agents in mechanically ventilated patients: a single centre, prospective observational study.

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In my case

And now…. I have to build it!!!

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Final Product!!

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