



Actions required for research protocols & analysis plans impacted by COVID-19

Dr Julie Marsh

Senior Research Fellow, Telethon Kids Institute

12 June 2020

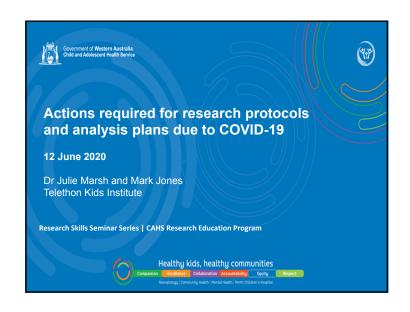
Research Skills Seminar Series | CAHS Research Education Program Research support, development and governance

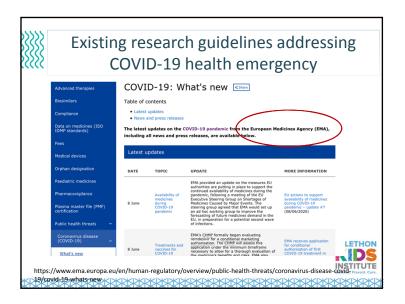


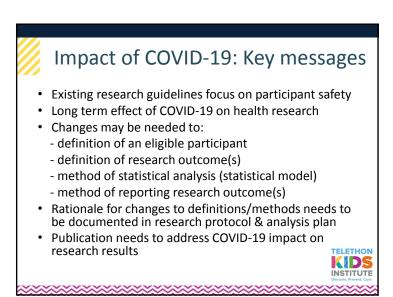


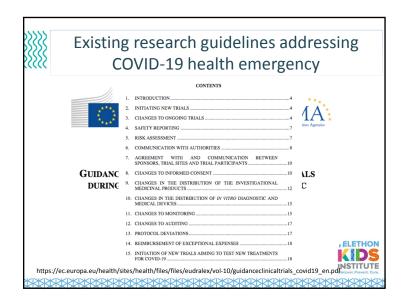
© CAHS Research Education Program, Department of Child Health Research, Child and Adolescent Health Service, WA 2020

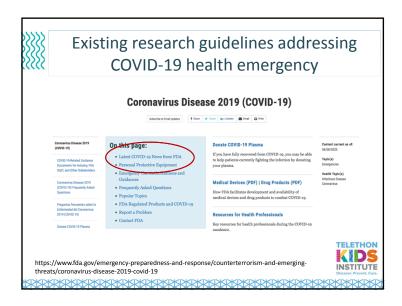
Copyright to this material produced by the CAHS Research Education Program, Department of Child Health Research, Child and Adolescent Health Service, Western Australia, under the provisions of the Copyright Act 1968 (C'wth Australia). Apart from any fair dealing for personal, academic, research or non-commercial use, no part may be reproduced without written permission. The Department of Child Health Research is under no obligation to grant this permission. Please acknowledge the CAHS Research Education Program, Department of Child Health Research, Child and Adolescent Health Service when reproducing or quoting material from this source.



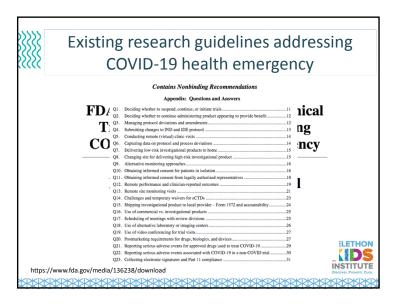


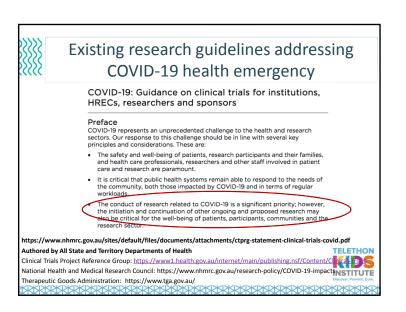








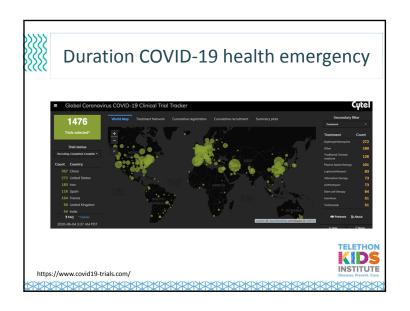






Existing research guidelines addressing COVID-19 health emergency

- Existing guidelines address the rights, safety and wellbeing of participants
- Evolving situation
- Pragmatic solutions required
- Address underlying changes in population, such as lifestyle, patterns of medical presentation & monitoring, social distancing and mixing (including travel), in addition to adherence/availability of intervention.





? ? ? ? ?

Duration COVID-19 health emergency

- Initial assumption of simple pre, during and post COVID-19 periods no longer valid
- Dates of COVID-19 'lock-down' are region specific and vary in content as case numbers or
- Individual adherence to 'lock-down' may vary due to social, cultural or country norms
- A simple stratified analysis to account for the impact of COVID-19 may not suffice





Impact COVID-19 on research objectives

The impact of COVID-19 on the research objectives can be roughly classified as issues related to:

- Treatment adherence: disruption to availability, delivery, access or administration of intervention or non-compliance ("holiday") from planned therapy, which may dilute treatment effect
- Recruitment: slow, suspended, stopped or extended recruitment at sites or by subgroups, which may affect the results for interim analyses and any response-adaptive algorithms

Considerations for changes to the research protocol or analysis plan

- Title, authors, and version control (note: relevant for changing state of the pandemic)
- Summary of study design and status
- Study period definitions
 - Adequately record definitions and values for the pre-pandemic and stages of post pandemic periods





Impact COVID-19 on research objectives

- Protocol violations: may increase compared to pre-COVID period, which may increase variability in outcome measures
- Missing data: disruption to visit/contact/assessment structure or missed visits, which would increase the need for imputation methods and decrease the precision of the statistical model estimates (including treatment effect)
- Potential bias: changing participant demographics (recruitment or withdrawals) or adherence (due to media coverage) over time
- Potential confounders: changes to trial eligibility over time
 and exposure to other investigational drugs and
 interventions

>>>>

Considerations for changes to the research protocol or analysis plan

- Summary of imminent actions
 - Data collection
 - Study conduct
 - Statistical analysis plan
 - Interim analysis
 - Sample size/ Power/ Trial operating characteristics
 - Important communications (who needs to know what and when?)
 - Data and Safety Monitoring Board interactions
 - Other: (statistical topics in) protocol amendments, ethics applications, update to approved/ published then statistical analysis plan

}

Considerations for changes to the research protocol or analysis plan

- Changes to the planned study conduct
 - Recruitment: recruitment halted, postponed, suspended, alternative means of recruitment
 - Data collection: follow-up halted, study visits planned to be skipped, different ways of collecting data, additional data to accurately characterise the study population under the new environmental setting, additional safety data and data for characterising deviations and adverse events
 - Intervention arms: study drug unavailable for new participants, study drug interrupted for ongoing participants, different delivery mode of the intervention, change in usual/standard care of the control arm
 - Outcomes (changes in definition or new outcomes)



Considerations for changes to the research protocol or analysis plan

- Potential solutions
 - Data collection: collect additional data on why visits missed, suspected/confirmed COVID-19 infection, amended data collection for adverse events, collect longitudinal data to account for missed visits, trim data collection if apprioriate
 - Study conduct: wider study visit windows to reduce protocol violations
 - Statistical analyses: consider longitudinal analyses and pre-specify sensitivity analyses to account for missing data and other impacts of COVID-19, revision or adding interim analyses, adjustments for confounders or time-interactions
 - Sample size/ Power/ Trial operating characteristics: reassess
 - Data and Safety Monitoring Board reviews: additional meetings, additional roles, establishing one DSMB if necessary, revisions to the DSMB membership to include more experts, revisions to the DSMB charter
 - Other: e.g. validation online vs face to face assessments or measurements





Considerations for changes to the research protocol or analysis plan

- Impact on the planned study design/methods
 - Population: change in study population and/or environment – changes in context can readily influence treatment response, especially in behavioural interventions
 - Outcome: change in definition or measurement
 - Intercurrent events: missing data due to COVID-19, death due to COVID-19, drug-holidays, concomitant COVID-19 medication, study withdrawal
 - Blinding: impacted by drug shortage and safety monitoring
 - Adherence or access to intervention





Documenting changes to the protocol

Included a section in the protocol that documents the anticipated effects of the COVID-19 health emergency on the research project and the approach taken to minimum protocol violations, bias and confounding.

Updates may be necessary to:

- Definition of outcome(s)
- Definition of eligible individuals
- Changes to visit structures
- Methods of data collection
- Etc.



Documenting changes to the analysis plan

Included a section in the analysis plan that documents the anticipated effects of the COVID-19 health emergency on the collection, outcomes, analysis and reporting of the research.

Updates may be necessary to:

- Definition of outcome(s)
- Definition of eligible individuals for the analyses
- Inclusion of missing data in the analyses
- Inclusion and reporting of inter-current events
- Method of analysis / sensitivity analyses
- Method of reporting

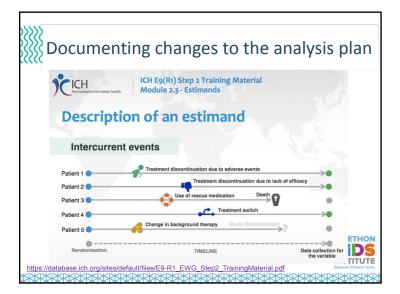


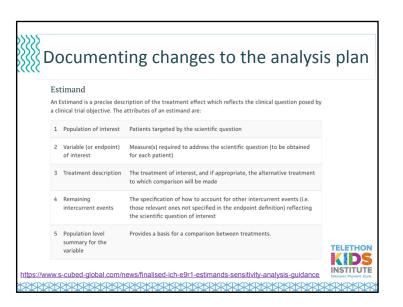
Documenting changes to the analysis plan

As we change eligibility, coding of the endpoint, treatment of inter-current events and choice of (population-level) summary statistic so we change the question that is being asked. Hence, similar trials can produce different, potentially conflicting, results.

Estimands: "bridge the gap between study objectives and statistical methods."







Documenting changes to the analysis plan

If the main analysis is specified ignoring the impact of COVID-19 on the outcome, then supporting sensitivity analysis should be defined that do account for this potential impact.

Within the **estimand** framework, sensitivity analyses can be defined that account for region and timedependent interactions. It is possible that over time these sensitivity analyses may need to be updated.

Questions?

Upcoming Research Skills Seminars:

26 Jun **Consumer and Community Involvement**

Annie McKenzie AM

Data Collection and Management 31 Jul

A/Prof Sue Skull

Please give us feedback!

Complete online survey via:

https://redcap.telethonkids.org.au/redcap/surveys/?s=PHAT99MPL3

*Full 2020 seminar schedule in back of handouts





Impact of COVID-19: Key messages

- Existing research guidelines focus on participant safety
- Long term effect of COVID-19 on health research
- Changes may be needed to:
- definition of an eligible participant
- definition of research outcome(s)
- method of statistical analysis (statistical model)
- method of reporting research outcome(s)
- Rationale for changes to definitions/methods needs to be documented in research protocol & analysis plan
- Publication needs to address COVID-19 impact on research results





KEY WEBSITES

1. Existing research guidelines addressing COVID-19 health emergency

European Medicines Agency (EMA) research guidelines addressing COVID-19 health emergency

https://www.ema.europa.eu/en/human-regulatory/overview/public-health-threats/coronavirus-disease-covid-19/covid-19-whats-new

EMA Guidance in the management of clinical trials during the COVID-19 pandemic

https://ec.europa.eu/health/sites/health/files/files/eudralex/vol-10/guidanceclinicaltrials covid19 en.pdf

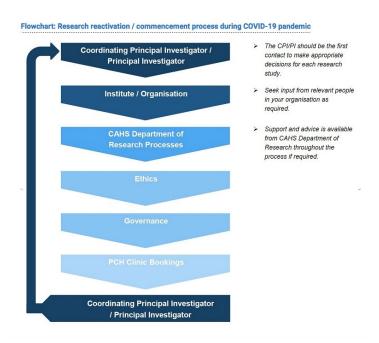
Latest COVID-19 News from FDA

https://www.fda.gov/emergency-preparedness-and-response/counterterrorism-and-emerging-threats/coronavirus-disease-2019-covid-19

FDA Guidance on Conduct of Clinical Trials of Medical Products during COVID-19 Public Health Emergency

https://www.fda.gov/media/136238/download

CAHS Research during COVID-19 pandemic



https://cahs.health.wa.gov.au/Research/COVID19-and-research-processes

https://www.cahs.health.wa.gov.au/Research/For-researchers/Support-for-researchers

All State and Territory Departments of Health

https://www.nhmrc.gov.au/sites/default/files/documents/attachments/ctprg-statement-clinical-trials-covid.pdf

2. Duration COVID-19 health emergency

COVID-19 Dashboard by the Center for Systems Science and Engineering (CSSE) at Johns Hopkins University (JHU)

https://coronavirus.jhu.edu/map.html

Global Coronavirus COVID-19 Clinical Trial Tracker

https://www.covid19-trials.com/

3. Documenting changes to the analysis plan

Finalised ICH E9(R1) Estimands and Sensitivity Analysis Guidance

https://www.s-cubed-global.com/news/finalised-ich-e9r1-estimands-sensitivity-analysis-guidance

Consumer and Community Involvement

Friday, 26 June 2020 | 12:30 - 1:30PM

Every researcher should be actively involving consumer or community members to improve quality and increase impact of their research.

Community involvement is increasingly a requirement for funding agencies and this seminar provides a practical introduction to the foundations of consumer and community involvement.

This seminar will cover basic principles of community and consumer involvement, the benefits and barriers, and what to put in place to get started.



Anne McKenzie AM

McKenzie AM is the Community Engagement Manager at Telethon Kids Institute. She was the former Head of the Consumer and Community Health Research Network which is an enabling platform of the WA Health Translation Network. Anne is a senior consumer representative for state and national health committees and former Chair of the Health Consumers Council WA. In 1994 Anne established the inaugural role of the Parent Advocate at PMH and has a long history of consumer advocacy with WA health services.

Perth Children's Hospital
PCH Auditorium
Level 5
(Pink or Yellow lifts)
15 Hospital Ave, Nedlands

Register Online

ResearchEducationProgram .eventbrite.com

*Hosted VC Sites Include:
CAHS – Community Health (WASON)
Fiona Stanley Hospital
Joondalup Health Campus
Lions Eye Institute
Royal Perth Hospital

*Online access via Scopia available

Further information:

E: ResearchEducationProgram@health.wa.gov.au

W: cahs.health.wa.gov.au/Research/

Go to "For Researchers" then "Research Education Program" https://cahs.health.wa.gov.au/en/Research/Forresearchers/Research-Education-Program





CAHS Research Education Program | Research Skills Seminar Series 2020

All sessions held on Friday 12:30 - 1:30pm, Perth Children's Hospital Auditorium

	Date	Topic (abbreviated titles)	Presenter
1	Feb 14	Research Fundamentals: Question and Protocol Development	A/Prof Sue Skull
2	Feb 21	Research Governance	Sunalene Devadason Helen Hughes
3	Mar 6	Introduction to Good Clinical Practice	Natalie Barber
4	Mar 13	Scientific Writing	A/Prof Sue Skull
5	Mar 27	Building your Personal Brand as a Researcher: How to get started and maintain momentum on social media	Dr Kenneth Lee
6	May 1	Survey Design and Techniques – 2019 version made available	A/Prof Sue Skull
8	May 15	Introduction to Adaptive Trials	Prof Tom Snelling
9	May 18	Coordination of COVID-19 Research in WA	Prof Gary Geelhoed
	May 22	Knowledge Translation – 2019 version made available	Fenella Gill/Tobias Schoep
10	Jun 5	Introductory Biostatistics: Understanding and reporting research results including P-Vales and Confidence Intervals	Dr Julie Marsh
11	Jun 12	Information for Clinical Triallists during COVID-19	Dr Julie Marsh
12	Jun 26	Consumer and Community Involvement	Anne McKenzie AM
13	Jul 31	Data Collection and Management	A/Prof Sue Skull
14	Aug 14	Oral Presentation of Research Results	A/Prof Sue Skull
15	Aug 28	Media and Communications in Research	Elizabeth Chester
16	Sep 11	Conducting Systematic Reviews	Prof Sonya Girdler
17	Sep 18	Involving the Aboriginal Community in Research	Glenn Pearson A/Prof Sue Skull
18	Oct 16	Rapid Critical Appraisal of Scientific Literature	A/Prof Sue Skull
19	Oct 23	Sample Size Calculations	Dr Julie Marsh
20	Nov 13	Grant Applications and Finding Funding	A/Prof Sue Skull
21	Nov 27	Qualitative Research Methods	Dr Shirley McGough
22	Dec 4	Ethics Processes for Clinical Research in WA	A/Prof Sue Skull

Topics may be subject to change; email notice will be provided.

All seminars and corresponding handouts are regularly revised and updated.

Attendance certificates are available upon request.

E: ResearchEducationProgram@health.wa.gov.au W: CAHS Research Education Program (external site)



Healthy kids, healthy communities





https://cahs.health.wa.gov.au/ResearchEducationProgram/

