THE UNIVERSITY OF MELBOURNE

Australian Government
Department of Health
Therapeutic Goods Administration

Rapid cycle drug safety evaluations using routinely collected data

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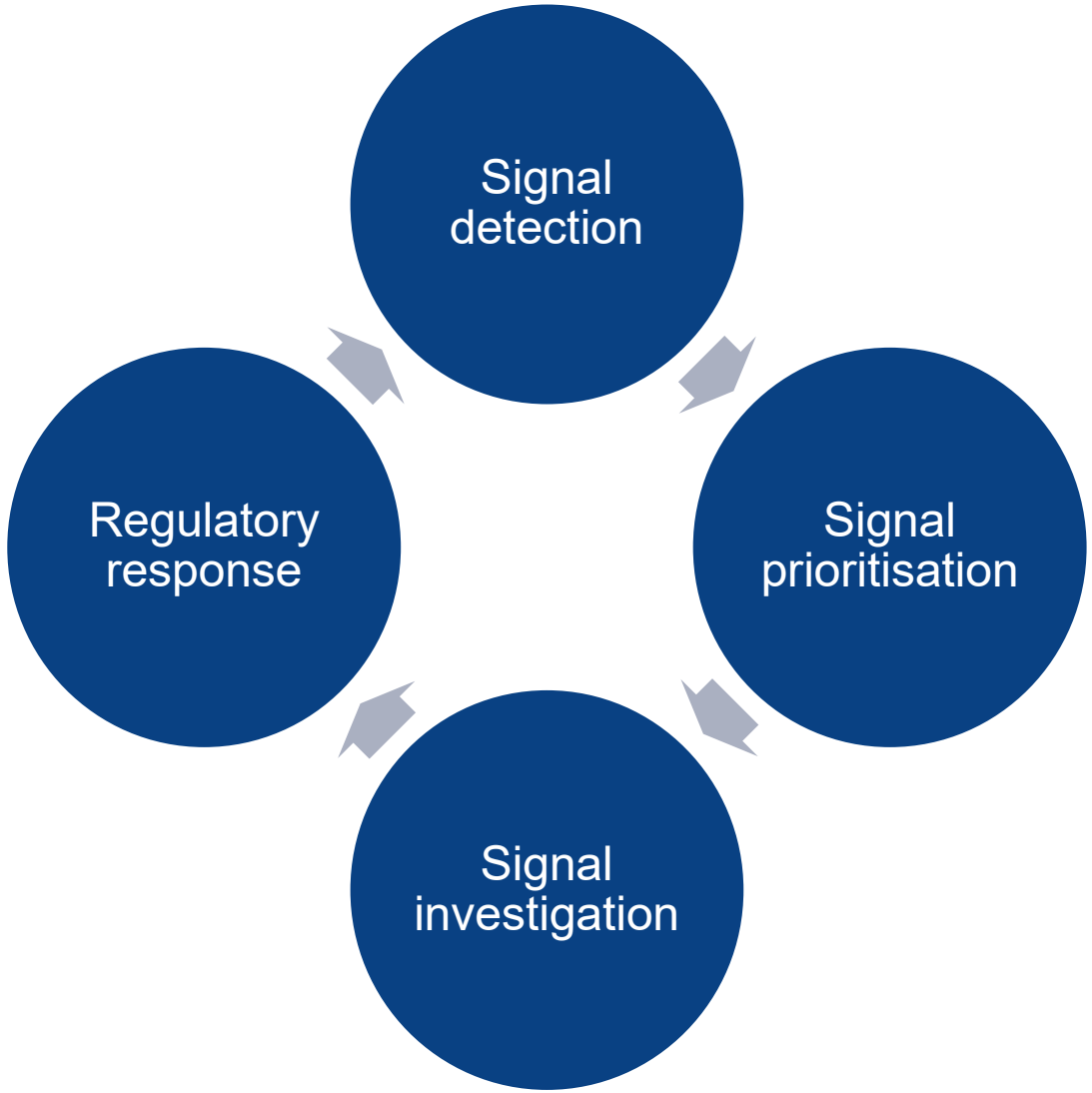
Overview

- Background and rationale
- Process outline
- Real-world examples

Background

- Traditional path for safety signal detection and investigation

- Population-level data provides real-world utilisation
  - Good for confirmatory analyses



High level feasibility analysis

- Leverage existing health service utilisation data to quickly generate evidence

- High-level analyses of exposed cohorts can be informative:

(1) Too few exposed cases

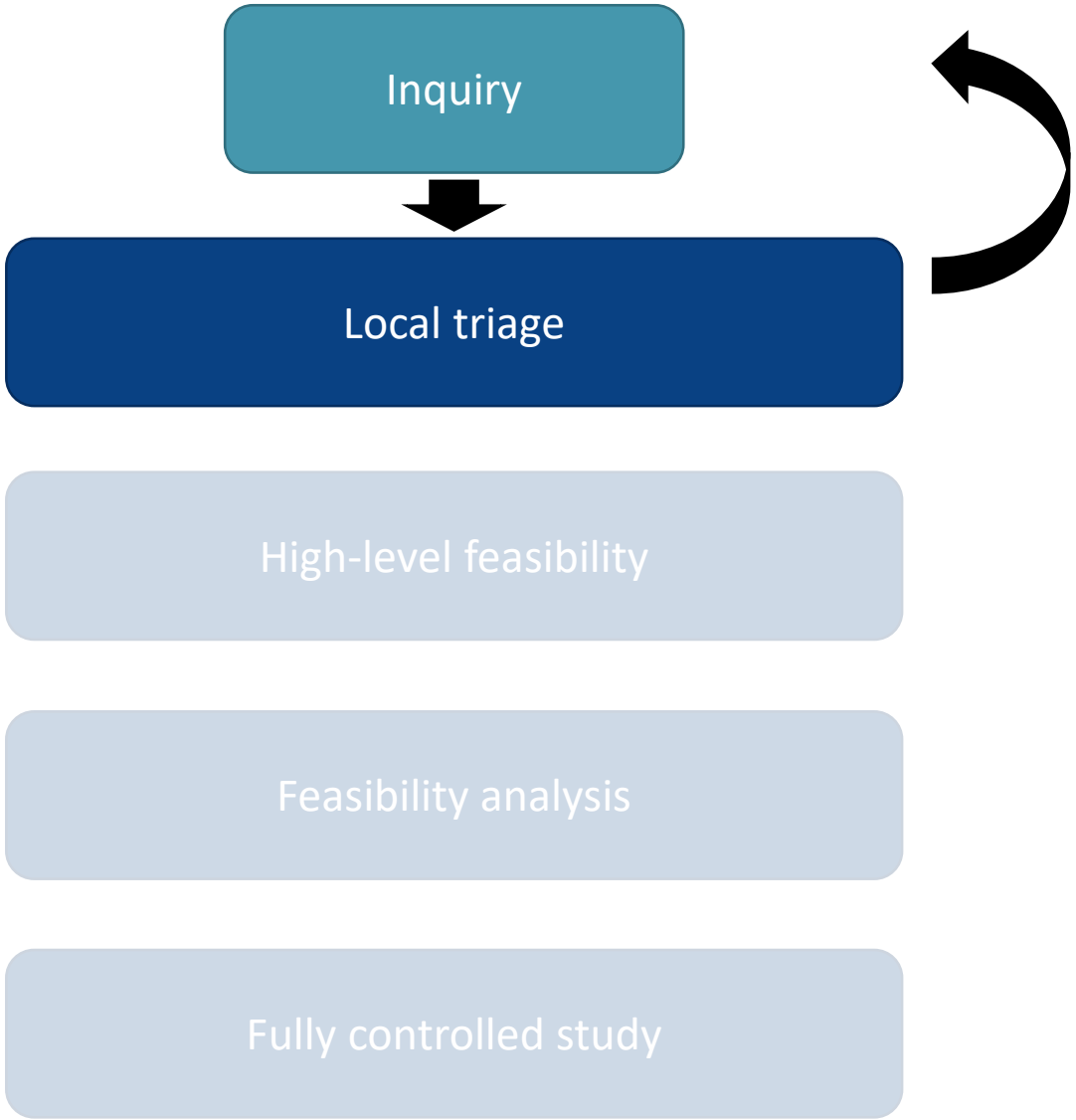
(2) Too few outcomes among exposed cases

(3) Potential signal (confirmed by crude RR)

Why not Australian data?

- Effects of drug are location-independent
- (Potentially) More years of information
- (Potentially) More data
- Prescribing practices may be similar
- Connections with external networks (e.g. CNODES, Health Canada, FDA)

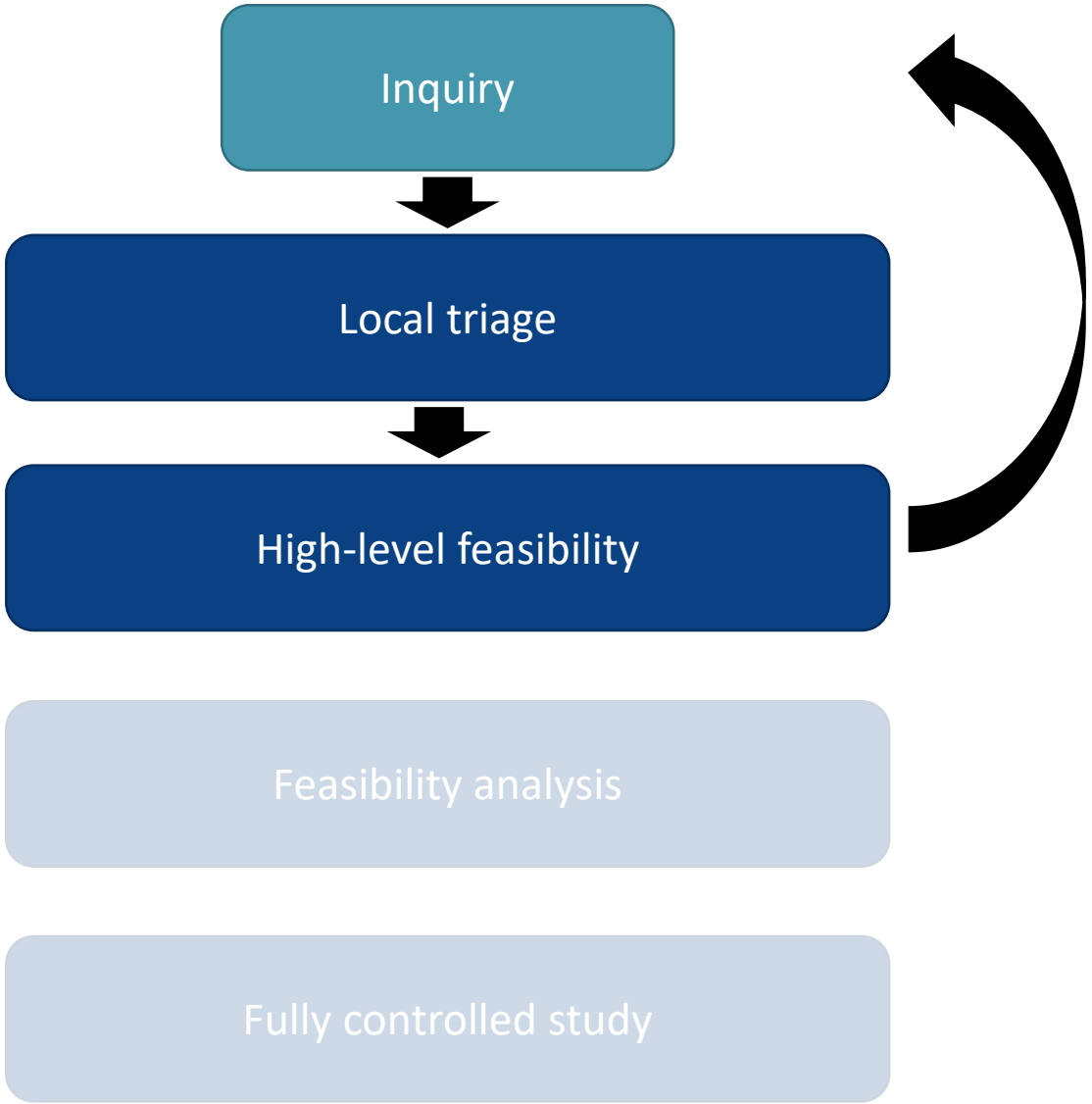
How it works



Turnaround time: **< 1 week**

High level assessment
(based on local knowledge)

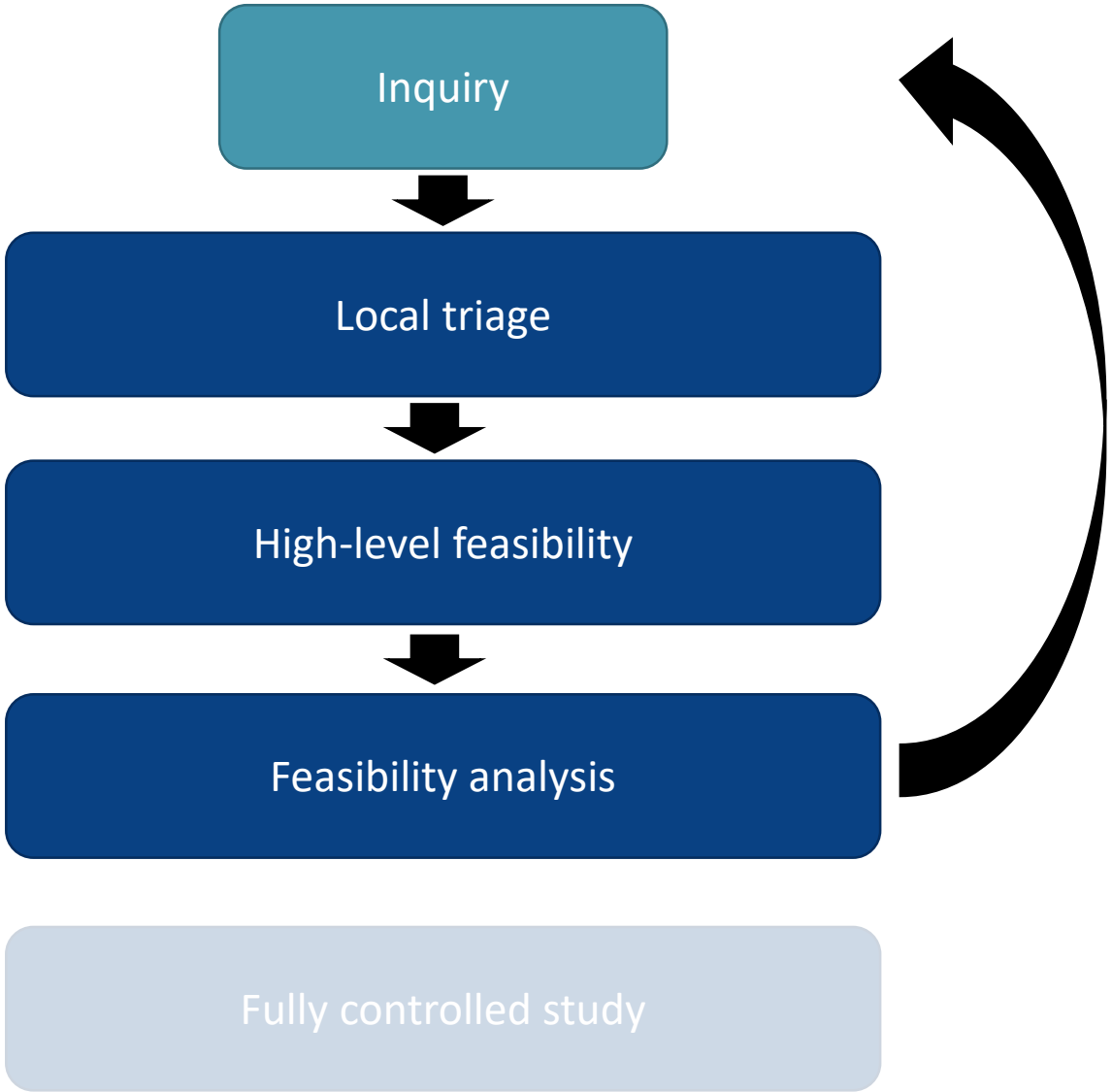
How it works



Turnaround time: **1 week**

- Evaluation of ongoing work
- Rx listing status
- Number of Rx

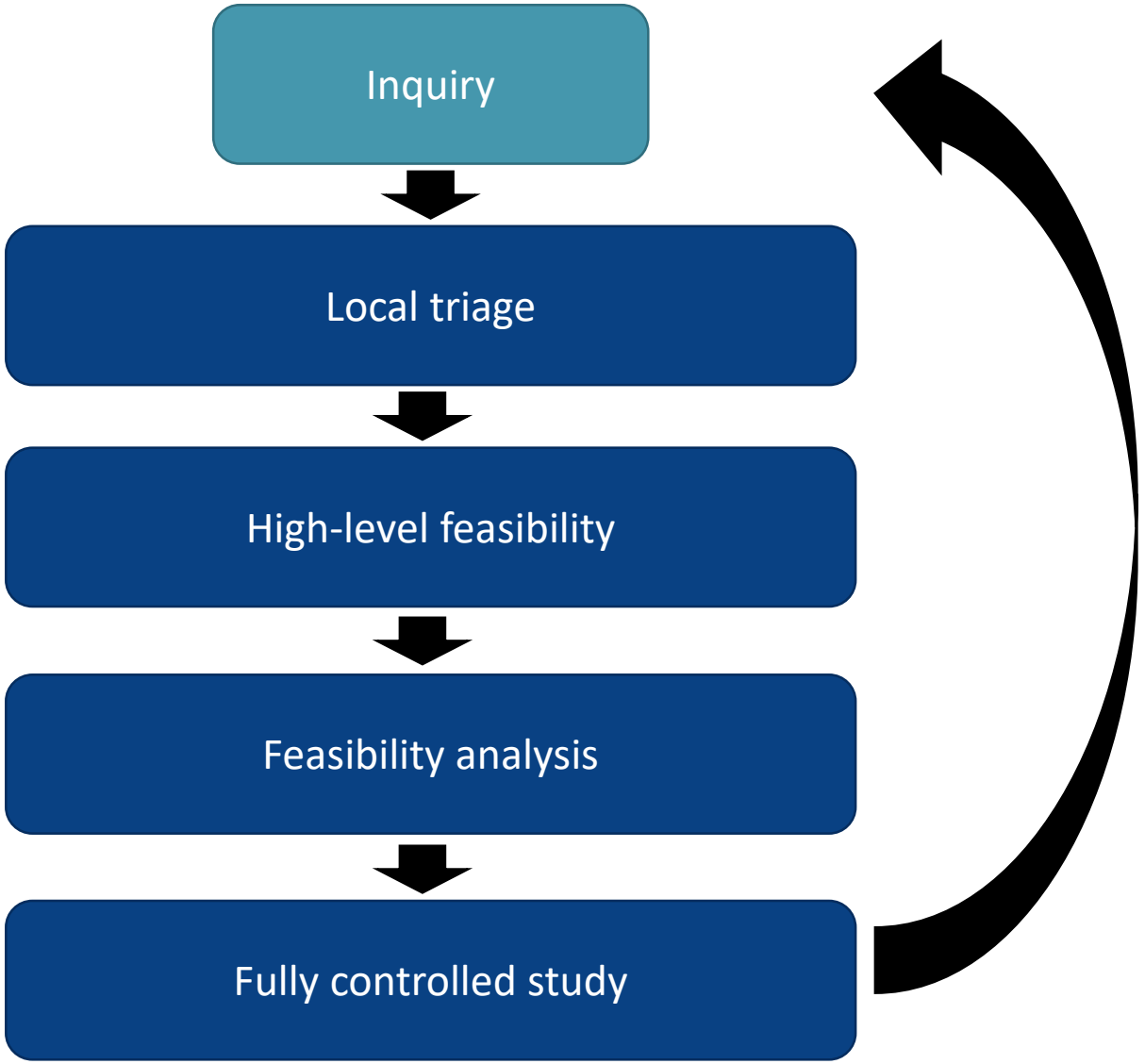
How it works



Turnaround time: **2-4 weeks**
(<40h analyst time)

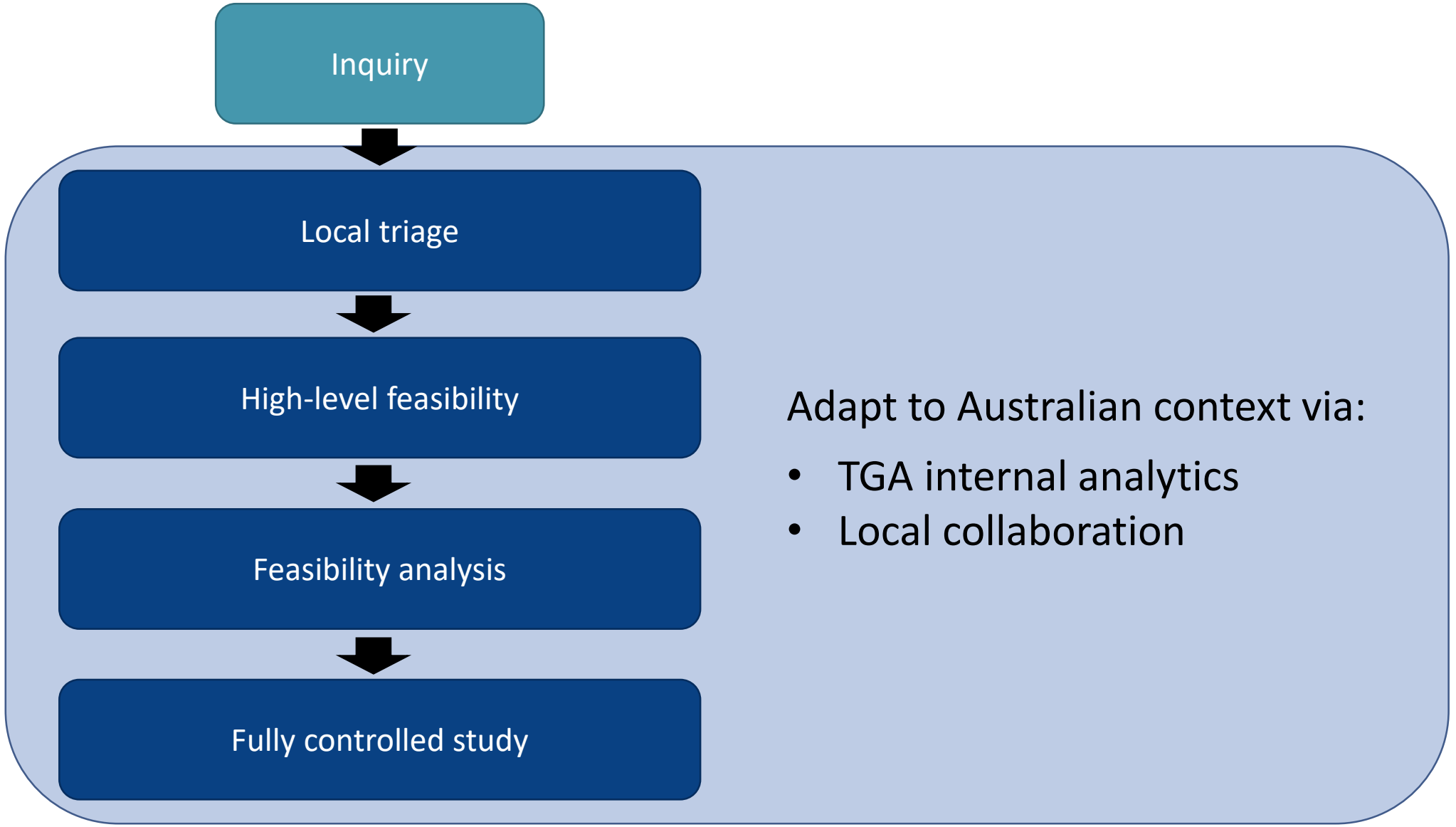
- No. exposures and outcomes
- Crude measures of association

How it works



Turnaround time: **4-8 mo.**

How it works

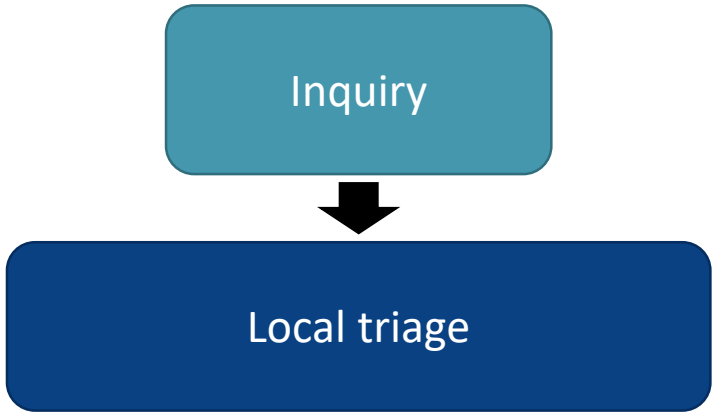


Adapt to Australian context via:

- TGA internal analytics
- Local collaboration

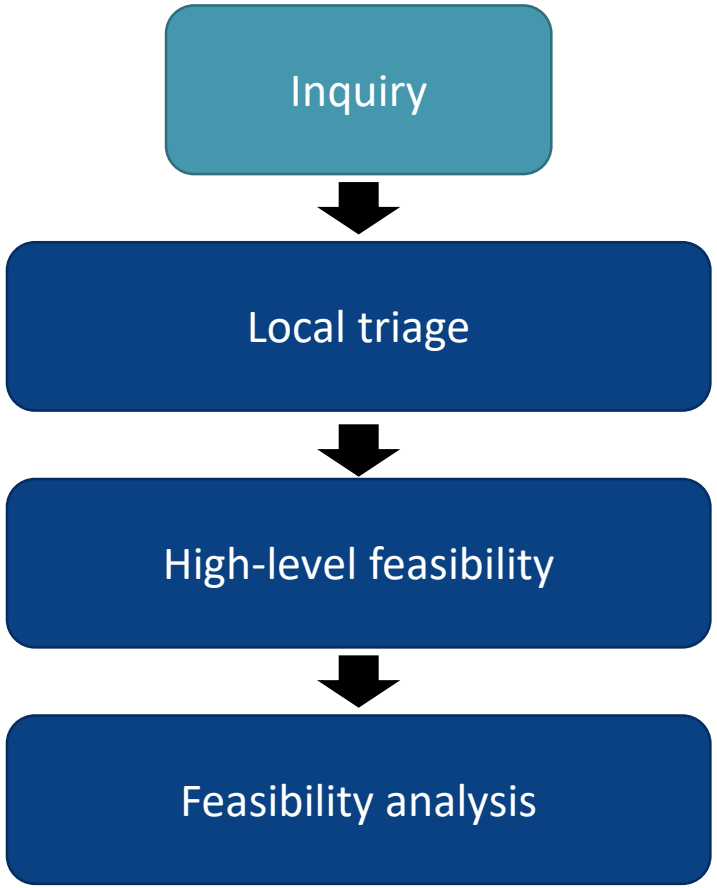
Applications

Temozolomide and heart failure (1)



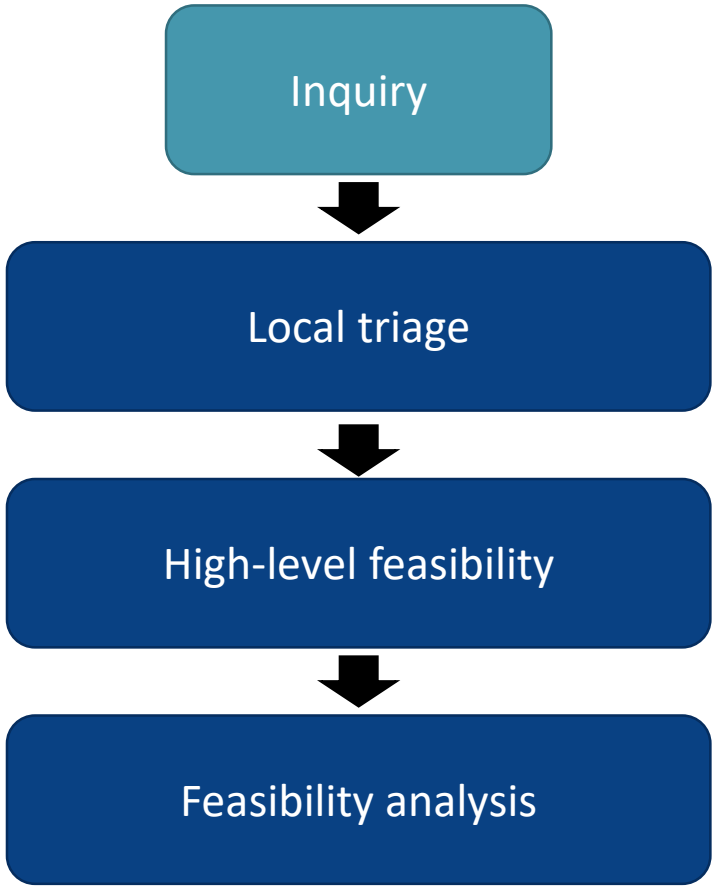
- PSSA → excess prescriptions for HF medication in patients initiating temozolomide
- Temozolomide use confined to patients with glioblastoma and astrocytoma
- No evidence in literature

Temozolomide and heart failure (2)



- Cohort definition: any temozolomide Rx between 1 April 2002 – 31 March 2016 (HF-naïve patients)
- Follow-up: 1 year
- Outcomes:
  - Primary: hospitalisation for HF (MRDx)
  - Sensitivity: newly-diagnosed HF (validated definition)
  - Secondary 1: hospitalisation or ED for HF (MRDx)
  - Secondary 2: all-cause mortality

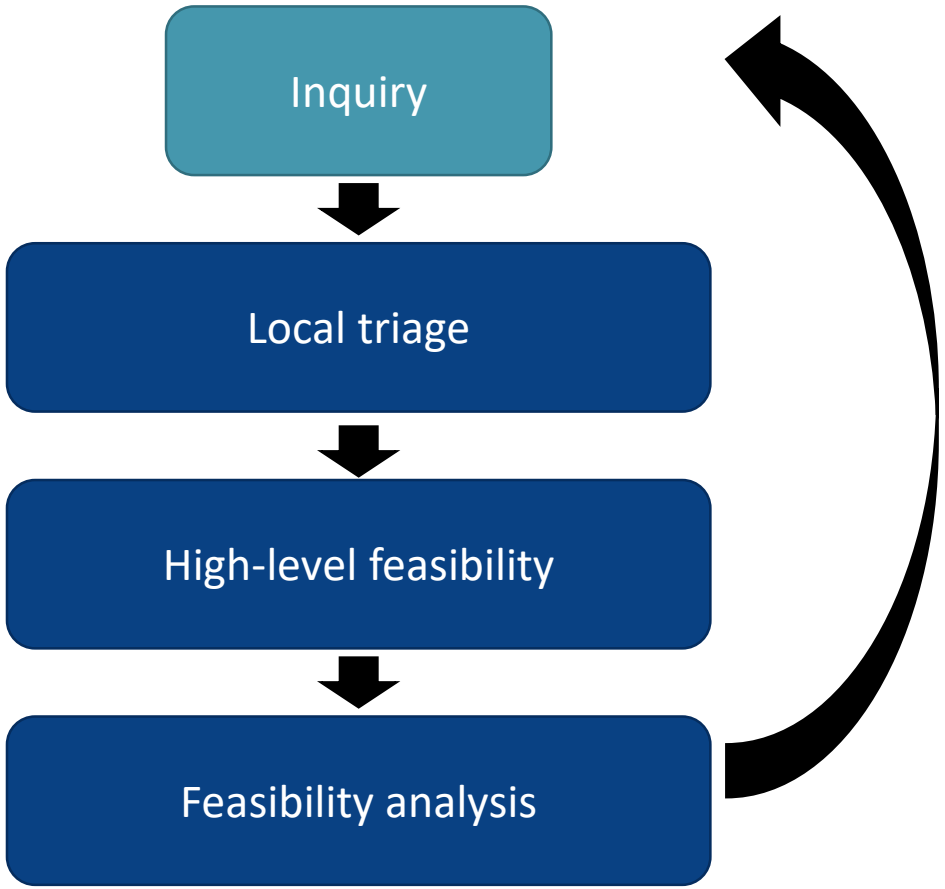
Temozolomide and heart failure (3)



	Number exposed	Number of events
Primary outcome		
Hospitalisation for heart failure (HF)	4,204	≤5
Secondary outcomes		
Hospitalisation or ED visit for HF	4,204	10 (0.24%)
Death	4,204	2,035 (48.4%)
Sensitivity Analysis		
New diagnosis of HF[1]	4,204	53 (1.26%)

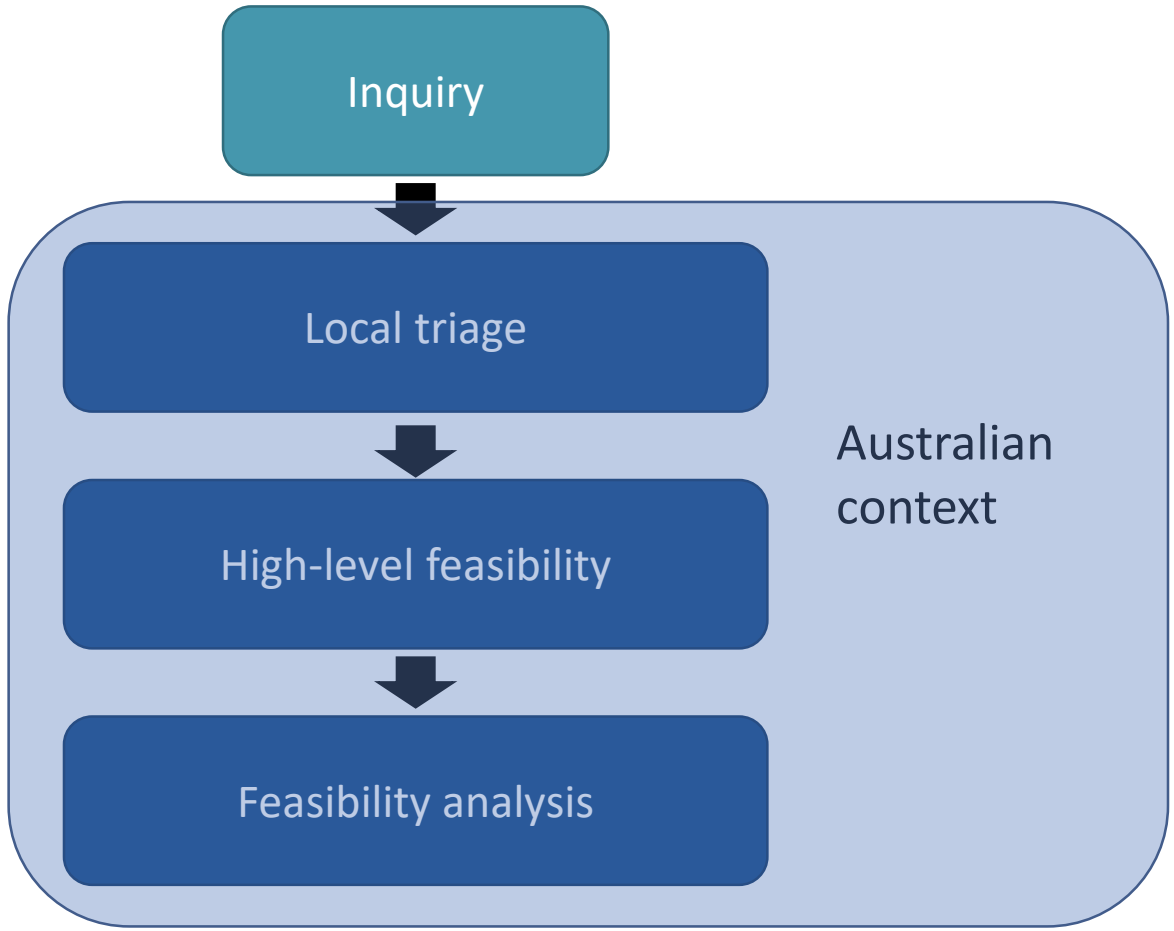
[1] ICES validated definition: 1 hospitalisation for HF OR 1 outpatient physician/ED visit for HF + 1 record with a HF diagnosis from any source within 1 year

Temozolomide and heart failure (4)



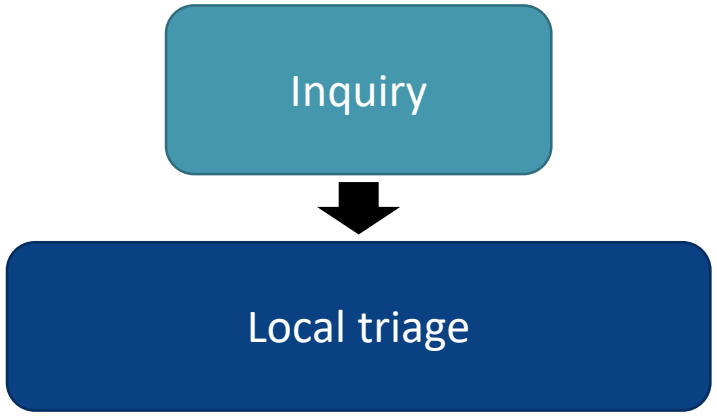
- Feasibility analysis was sufficient
  - Number of HF outcomes too low to warrant progression to a controlled study
  - Difficult to select an appropriate control group (limited indication for temozolomide)
  - Competing risks
- Final report submitted to TGA

Temozolomide and heart failure (5)



- Protocol adapted to AUS data
  - Co-designed with TGA analyst / epidemiologist
- Analysis undertaken using available data from Department of Health
- Low numbers of exposed cases
  - Conclusions unchanged

Psychostimulants and pregnancy (1)

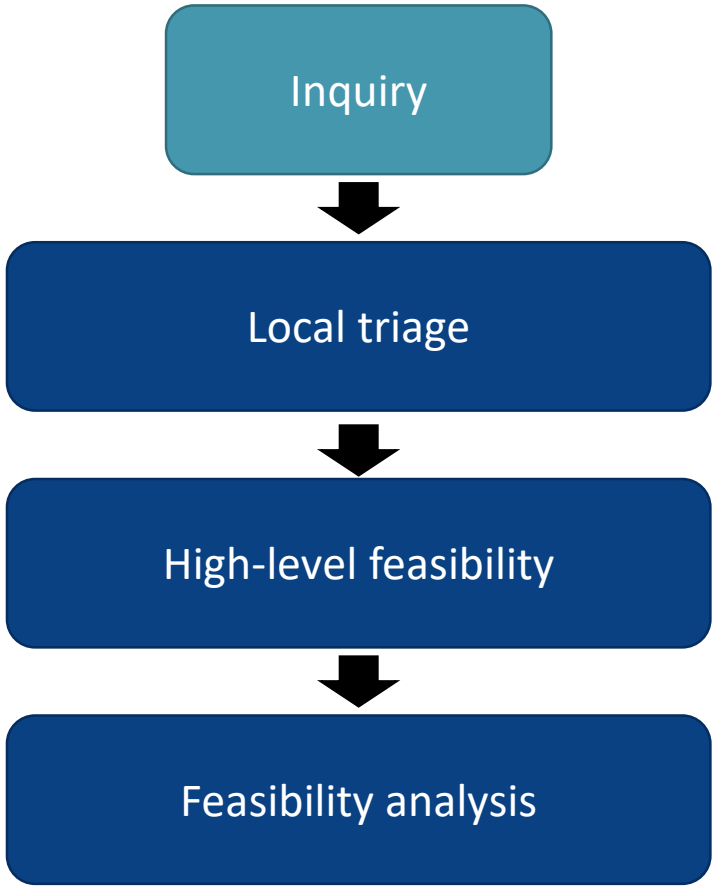


- Recent evidence suggested association between psychostimulants and adverse pregnancy and birth outcomes
- Uncertainty in evidence => need for confirmatory analysis using population-level data

Cohen JM et al. Placental Complications Associated With Psychostimulant Use in Pregnancy. Obstetrics & Gynecology. 2017;130(6).

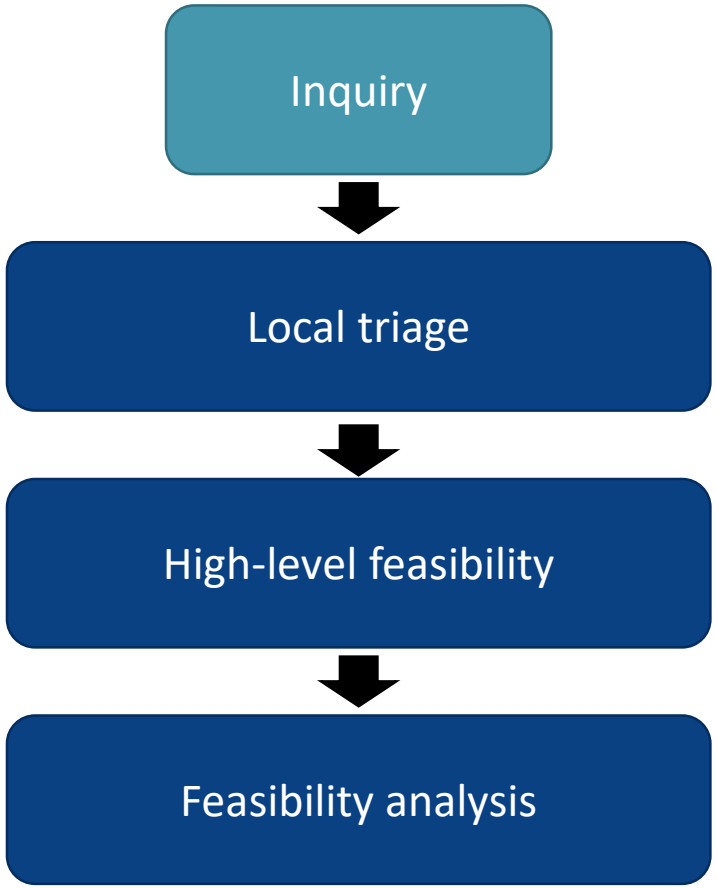
Huybrechts KF et al. Association between methylphenidate and amphetamine use in pregnancy and risk of congenital malformations: A cohort study from the international pregnancy safety study consortium. JAMA Psychiatry. 2018;75(2):167-75

Psychostimulants and pregnancy (2)



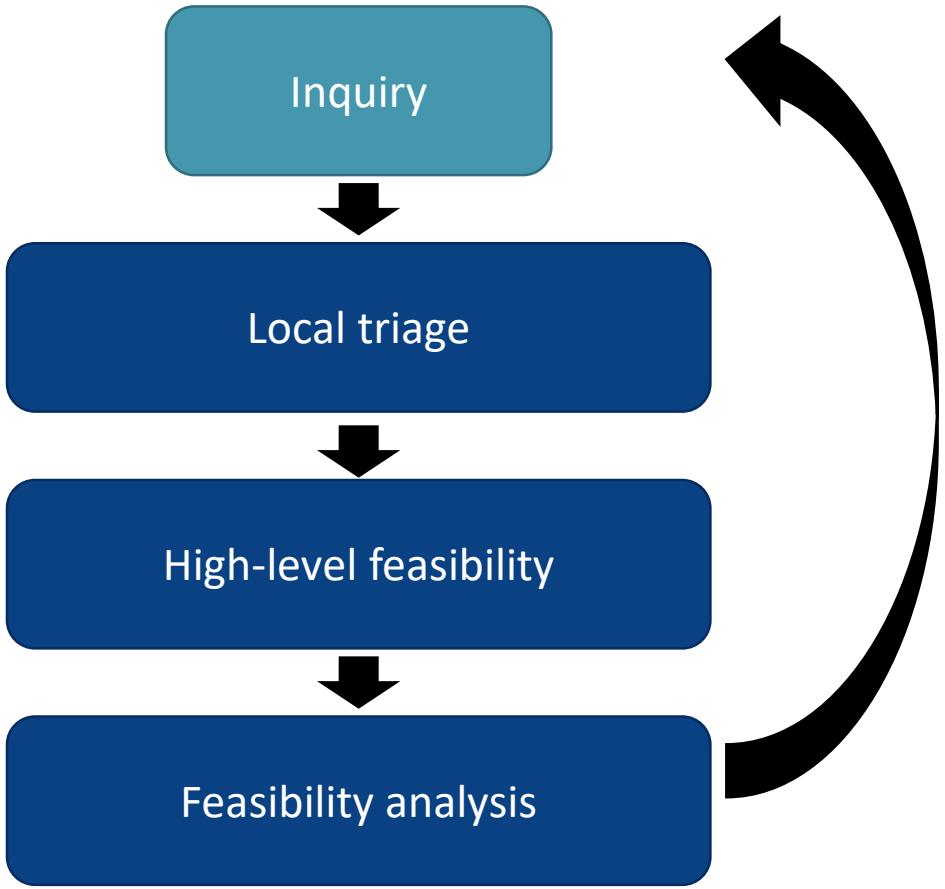
- Study population: singleton deliveries conceived between 1 July 2012 and 31 March 2016
- Exposure: 1+ Rx for psychostimulant (methylphenidate, amphetamine, dextroamphetamine, lisdexamfetamine) overlapping pregnancy
- Pregnancy outcomes: gestational DM, preeclampsia, placental abruption, pre-term birth
- Birth outcomes: stillbirth, low birthweight, small / large for gestational age, congenital anomalies, admission to NICU, newborn seizures

Psychostimulants and pregnancy (3)



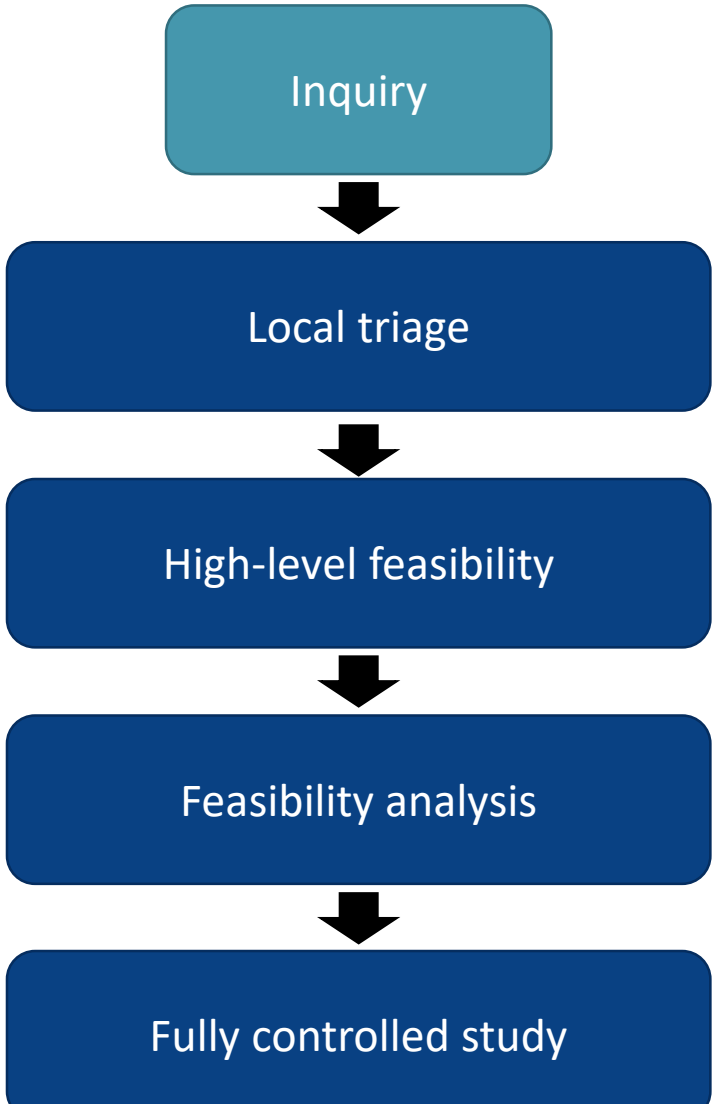
All singleton deliveries	449,499
Number exposed	1,346
	Crude RR (95% CI)
Pregnancy outcomes	
Gestational DM	0.98 (0.80, 1.20)
Preeclampsia	1.96 (1.48, 2.59)
Placental abruption	1.57 (1.02, 2.43)
Pre-term birth	1.68 (1.44, 1.96)
Birth outcomes	
Low birthweight	1.55 (1.29, 1.87)
Small for gestational age	1.05 (0.92, 1.20)
Large for gestational age	1.12 (0.94, 1.33)
Congenital anomalies	1.11 (0.93, 1.33)
Admission to NICU	2.13 (1.93, 2.34)
Newborn seizure	3.43 (1.85, 6.39)

Psychostimulants and pregnancy (4)



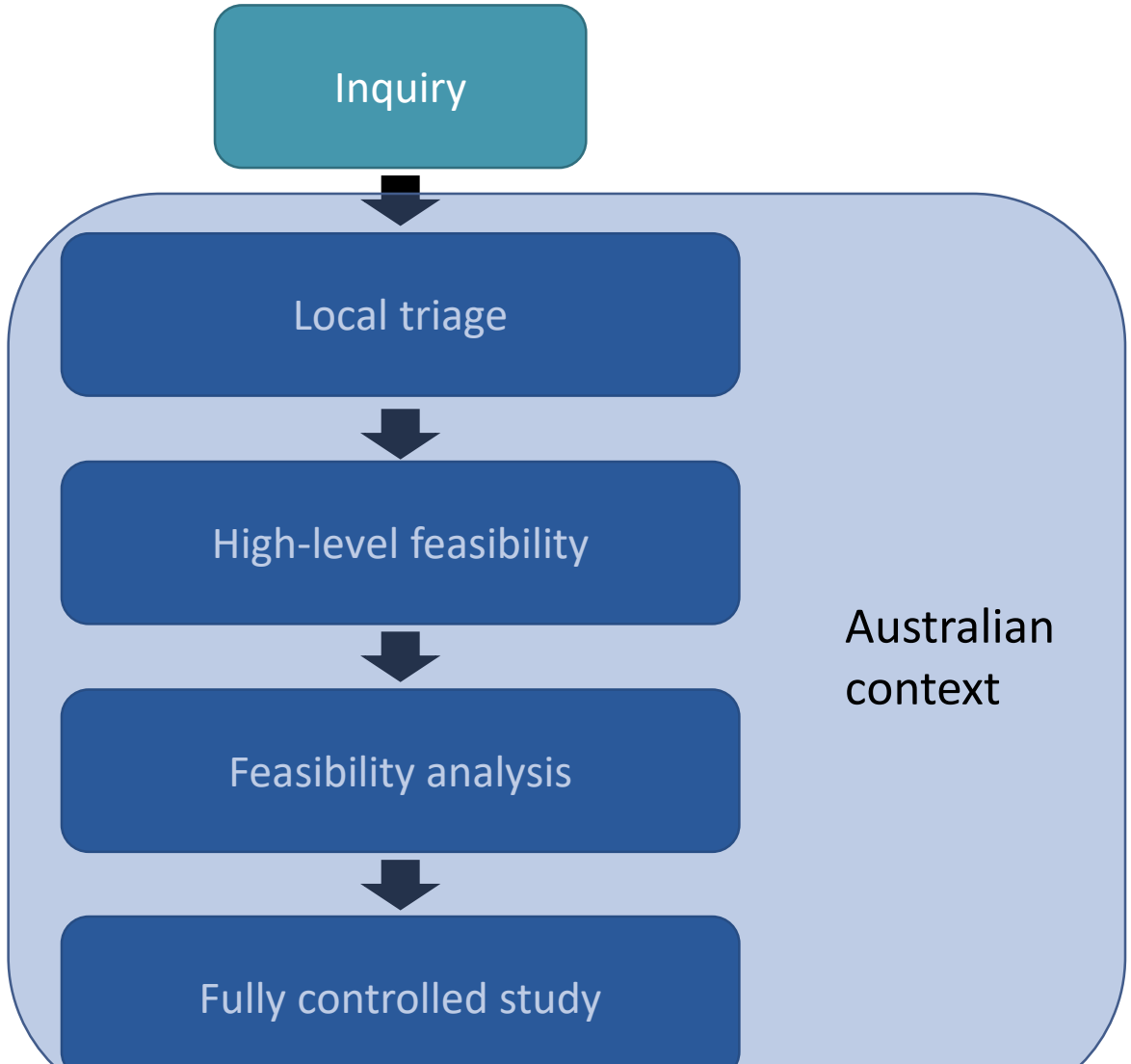
- Potential association between psychostimulants and pregnancy / birth outcomes
- Possible placental effect

Psychostimulants and pregnancy (4)



- Potential association between psychostimulants and pregnancy / birth outcomes
- Possible placental effect
- Further investigation needed → fully adjusted analysis *(in progress)*

Psychostimulants and pregnancy (5)



- Protocol adapted to AUS data
- Analysis underway using available data from UNSW

Key findings

Key findings

- Population-level data provides useful information
- Feedback and involvement is key
- Simultaneously building capacity within TGA
- Distil information in an easily-digestible package
- Win-win for policy and academia

Acknowledgements

- Brigitta Osterberger
- Yan Yu
- Jane Cook
- David Henry
- Sallie Pearson
- Michael Paterson
- Alys Havard
- Helga Zoega

Thank you