RAPID PROGAM - Request for waiver or exemption from Human Ethics Committee Review for a Quality Improvement Activity

Project title
RAPID Program - to evaluate the net clinical benefits and toxicities of medications and other non-pharmacological interventions commonly used in the palliative and supportive care.

Project type
- Quality improvement activity, patient safety research
- Multi-centre
- Negligible risk

Project summary
Aim
To evaluate the net clinical benefits and toxicities of medications and other non-pharmacological interventions commonly used in the palliative and supportive care disciplines.

Background
Palliative and supportive care has sought to improve its evidence base for clinical prescribing in a number of ways. Although there are high quality phase III randomised, controlled trials being done on pharmacological and other interventions around the world, these are expensive and complex, particularly if run over multiple Sites or countries. A complementary way of taking forward the evidence base is to include consecutive cohort studies that describe the net clinical effects of the medication or intervention under study.

The Palliative Care Clinical Studies Collaborative (PaCCSC) and Cancer Supportive Care Clinical Studies Collaborative (CSCCSC) are Australian based clinical research groups. PaCCSC/CSCCSC are located in IMPACCT: the Centre for Improving Palliative, Aged and Chronic Care through Clinical Research and Translation, Faculty of Health, the University of Technology Sydney (UTS).

Rigorously designed, double-blind, randomised controlled, multisite phase III studies conducted by PaCCSC/CSCCSC and multi-site patterns of care / pharmacovigilance studies have shown that there is systematic under-reporting of medication toxicity in palliative and supportive care. In order to address this gap, a program examining the use of key medications in palliative and supportive care has been developed. Whilst the program commenced primarily with the key aim of conducting pharmacovigilance research the adaptive methodology has been expanded into a range of non-pharmacological interventions where the evidence and patient safety outcomes are limited or not known.

Patient group(s)
The data included in this program is sourced from patients whose treating clinician has already made the clinical decision to prescribe the medication or intervention of interest. The collection of data does not precede this decision nor impacts the decision making process of the prescribing physician in anyway.

Series
The first series studied commenced in 2011, following the first protocol release. The program expanded in 2016 to include a range of medications across a number of symptom areas commonly experienced in palliative and supportive care including:

- pain,
- breathlessness,
- gut dysfunction,
- nausea,
- cognitive, mood and neurological disorders
- appetite and cachexia, and
- fatigue.

In 2016 the Investigators expanded the Program to include non-pharmacological interventions, including examples to date of red blood cell transfusions; hypodermoclysis and ascetic taps.

It is proposed to study one selected medication in each of the symptom nodes concurrently, and one non-pharmacological intervention series simultaneously with scope for post marketing series to be run concurrently as they arise. A table of past present and future, currently planned series has been provided (Table 1). This is an ongoing program of work and new medications, non-pharmacological interventions and post marketing series added over time.

Table 1: Past, present and future predicted RAPID series

Symptoms	Past series	Current series	Future
Pain	• Pregabalin for neuropathic pain *(Sanderson, et.al. 2014; Sanderson, et.al. 2016)* • Gabapentin for neuropathic pain *(Clark,et.al. 2015)*	• Amitriptyline for neuropathic pain • Oxycodone/Naloxone for Pain (Targin DE prescribing) • NSAIDS for Pain	
Breathlessness		• Benzodiazepines for breathlessness	• Morphine for breathlessness
Gut Dysfunction		• Macrogol for constipation	
Nausea	• Metoclopramide for nausea *(Currow, et.al. 2012)* • Dexamethasone for appetite /nausea *(Hatano, et.al. 2016)* • Haloperidol for nausea *(Digges, et. al. 2017)*	• Cyclizine for Nausea	
Cognitive, mood & neurological	• Haloperidol for delirium *(Crawford, et.al. 2013)*	• Midazolam for agitation	
Appetite & cachexia		• Mirtazapine for anorexia	
Fatigue			
Intervention	• Blood Transfusion *(To, et.al. 2017; To, et.al. 2016)* • Hypodermoclysis	• Ascitic Taps	• Venting gastrostomies • Pleural fluid drainage • Pleurodesis • Endoluminal stents • Intrathecal analgesia
Special interest & post-marketing series			• Gabapentin for Itch and Restless legs • Cannabis prescribing • Methadone conversion • Nursing interventions

Methods
Data will be collected following the treating clinicians decision to prescribe the intervention. This means that the therapeutic benefit, toxicity (drug/host), any significant drug/drug interactions, or patient safety implications can be prospectively collected by participating Sites worldwide and consolidated into reports that will directly inform clinical practice. The results of the completed studies have been made available through publication (Table 1) and presentations. Future series will be rapidly available to the sector using the same approach.

Information will be collected at three times points:

- Baseline (T0) - basic clinical data including broad diagnostic group, and basic clinical parameters (only if available) and demographic data (age, gender but no names, addresses or date of birth will be collected);
- A time point for clinical benefit (T1) – selected specifically for each series by the series subcommittee;
- A time to toxicity (T2) - a time point at which immediate and short term toxicities, if any, will be collected; and
- Adhoc data on toxicities that occur at any time point (within a defined reporting period per series) will also be collected.

Reasons for data missing at any of the three standard data points is also collected. Data is entered into REDCap via a computer or mobile phone App. REDCap is a secure web-based encrypted research data management system for which UTS holds a licence to use for research purposes. Data may be entered for up to 28 days for some interventions, although it is likely that the routine data points will be far sooner. No patient identifiable data will be collected.

Possible outcomes
The *primary outcome* is to evaluate the benefit and toxicity of medications and other non-pharmacological interventions commonly used in palliative and supportive care.

The *secondary outcomes* are to:

- describe the indications for medicines and interventions being used in supportive and palliative care; and
- document the frequency of prescribing of common medicines and other interventions in supportive and palliative care.

This program provides the opportunity to cost effectively study medications and other non-pharmacological interventions used in palliative and supportive care in a timely manner which will contribute to the evidence base in these populations both locally and internationally.

Project design
This is a series of prospective, consecutive cohort studies of people consecutively commenced on the medication for the symptom (indication) to capture best clinical practice by capturing net clinical benefit (toxicities and benefits).

Data collection techniques
Relevant data will be entered into REDCap by the medical officer caring for the patient or a paper-based Case Report Form will be completed by the medical officer and the data entered by a clinical

trial nurse. Data collection takes approximately five minutes at each of the three time points (baseline, clinical benefit point, clinical toxicity point).

Data to be collected
Key demographic and routine clinical information including age and gender are collected. No patient identifiable or re-identifiable data is collected with a computer generated identification number allocated to each consecutive case entered into REDCap. No additional pathology tests are requested and minimal documentation of the available tests is recorded when already available. No data beyond routine clinical practice is collected.

Number of patients
Sites may choose which series to be involved in dependent on local practice. It is requested that the Sites collect at least three patients per series they choose to be involved in however this number is not capped and Sites may enter data on more patients if they choose.

Tasks patients complete
No consent is required as patients are not required to complete any tasks or assessments. This program will collect only routine data from best clinical practice following the decision of the treating clinician to prescribe the medication or intervention under study. No identifying patient data is collected.

Analysis of results
Following each series closure, data collected from all participating Sites is aggregated and basic descriptive statistics and frequencies are used to determine rates of benefit and toxicity observed during the data collection period.

Likely benefits of the project for patients, institution and/or community
There are no direct benefits to patients whose data is collected as part of this program of work. However, it is feasible that those Sites participating in this program will be more attuned to possible benefits and risks from the intervention understudy and therefore more closely monitor their patients.

Institution benefits include being part of an international community of practice routinely assessing local clinical practice in line with international, consensus driven practice standards. Participating Sites who recruit to each series are acknowledged for their efforts in the publication of the results paper in the international peer reviewed literature.

This program allows the net clinical effect (therapeutic benefit/failure) to be identified and published on a regular basis in order to refine practice. Publication of the findings from each series include implications for practice as well providing information to inform national pharmaceutical policies around the world.

Actual or potential risk associated with the project
There are no foreseen risks associated with this program of quality improvement.

Research personnel

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Frequently asked questions

Consent
Will informed consent be obtained from patients?
No

Data and privacy
Is there a requirement for the project to collect, use, or disclose individually identifiable or re-identifiable data of a personal nature about patients without their consent?
No

Will individually identifiable data about patients be disclosed in the dissemination of research results?
No

Conflicts of interest
Are any 'conflict of interest' issues likely to arise in relation to this research?
No

Payments
Are there any payments made to Sites, personnel or patients for participation?
No.

Dissemination plan
How will the results be disseminated?
Data will be collated as soon as each series is closed and publication of the aggregated results will be in peer reviewed journals. This will include the background to the medication or other non-pharmacological intervention, its pharmacokinetic and pharmacodynamic properties, its registered indications and the way it has been used in palliative care. Benefits will be quantified as well as the toxicities that were encountered. Although Sites will be acknowledged for their individual participation in each series they contribute data to, there will be no way of identifying individual patients from any Site. Only de-identified data is collected which is then aggregated prior to its presentation in the peer reviewed literature.

Publications
Foundation Paper:
Currow DC, Rowett D, Doogue M, To THM, Abernethy AP. (2012) An international initiative to create a collaborative for pharmacovigilance in hospice and palliative care clinical practice. *Journal of Palliative Medicine, 15*(3):282–6. doi: 10.1089/jpm.2012.9605

Series Papers:
1. To T, LeBlanc TW, Eastman P, Neoh K, Agar MR, To LB, Rowett D, Vandersman Z, Currow DC. (2017) The Prospective Evaluation of the Net Effect of Red Blood Cell Transfusions in Routine Provision of Palliative Care. *J Palliat Med*. doi: 10.1089/jpm.2017.0072.
2. Digges M, Hussein A, Wilcock A, Crawford GB, Boland JW, Agar MR, Sinnarajah A, Currow DC, Johnson MJ (2017) Pharmacovigilance in Hospice/Palliative Care: Net effect of haloperidol for nausea or vomiting. *J Palliat Med*. doi: 10.1089/jpm.2017.0159
3. To TH, To LB, Currow DC. (2016) Can we detect transfusion benefits in palliative care patients? *J Palliat Med*. doi: 10.1089/jpm.2016.0073.

4. Agar MR, Quinn SJ, Crawford GB, Ritchie CS, Phillips JL, Collier A, Currow DC. (2016) Predictors of mortality for delirium in palliative care. *J Palliat Med*. doi: 10.1089/jpm.2015.0416
5. Hatano Y, Moroni M, Wilcock A, Quinn S, Csikós Á, Allan SG, Agar M, Clark K, Clayton JM, Currow DC. (2016) Pharmacovigilance in hospice/palliative care: the net immediate and short-term effects of dexamethasone for anorexia. *BMJ Supportive & Palliative Care, 6*(3):331-7. doi: 10.1136/bmjspcare-2015-001037
6. Sanderson C, Quinn SJ, Agar M, Chye R, Clark K, Doogue M, Fazekas B, Lee J, Lovell MR, Rowett D, Spruyt O, Currow DC (2016) Pharmacovigilance in hospice/palliative care: net effect of pregabalin for neuropathic pain. *BMJ Support Palliat Care. 6*(3):323-30. doi: 10.1136/bmjspcare-2014-000825
7. Clark, K, Quinn SJ, Doogue M, Sanderson C, Lovell M, Currow DC. (2015) Routine prescribing of gabapentin or pregabalin in supportive and palliative care: what are the comparative performances of the medications in a palliative care population? *Support Care Cancer*. 23(9):2517-20. doi: 10.1007/s00520-015-2837-z
8. Sanderson C, Quinn S, Agar M, Chye R, Clark K, Doogue M, Fazekas B, Lee J, Lovell M, Rowett D, Spruyt O, Currow D. (2014) Pharmacovigilance in hospice/palliative care: net effect of gabapentin for neuropathic pain. *BMJ Supportive & Palliative Care, 5*(3):273-80 doi: 10.1136/bmjspcare-2014-000699
9. Crawford GB, Agar M, Quinn SJ, Phillips J, Litster C, Michael N, Doogue M, Rowett D, Currow DC. (2013) Pharmacovigilance in Hospice/Palliative Care: Net Effect of Haloperidol for Delirium. *Journal of Palliative Medicine*, *16*(11):1-7. doi: 10.1089/jpm.2013.0230
10. Currow DC, Vella-Brincat J, Fazekas B, Clark K, Doogue M, Rowett D. (2012) Pharmacovigilance in hospice/ palliative care: Rapid report of net clinical effect of metoclopramide. *Journal of Palliative Medicine, 15*(10):1071-5. doi: 10.1089/jpm.2012.0111

Presentations

1. Currow, D., Rowett, D., Doogue, M., Brown, L., *RAPID - an international collaboration studying the benefits and harms of medicines and other interventions used in palliative care.* Australian Catholic HealthCare Conference, Mater Medication Research Institute, Brisbane, June 2018
2. Currow, D., Rowett, D., Doogue, M., Brown, L., Raymond, B. *Using everyday practice to inform and develop an evidence base for future practice – applying the RAPID Pharmacovigilance methodology in palliative care.* PCNA Conference, May 2018, Brisbane, Australia.
3. Devilee L, *New Evidence from Palliative Care Clinical Trials*. Palliative Care Conference, Brisbane. November 2016
4. Devilee L, Cosic C. *Participating in palliative care clinical research: RAPID makes it easy.* SAPC State Conference June 2014
5. Devilee L, *Participating in palliative care clinical research: RAPID makes it easy*. PCNA Conference April, 2014

Posters

1. Currow, D., Rowett, D., Doogue, M., Brown, L., Hunt, J. *Pharmacovigilance in hospice / palliative care*. National Medicines Symposium, Canberra Convention Centre, May/June 2018
2. L. Brown (formerly Devilee), D. Rowett, M. Doogue & D. Currow on behalf of the Palliative Care Clinical Studies Collaborative (PaCCSC). *The real world effects of prescribing in palliative care: RAPID*. Poster presented at the European Association for Palliative Care (EAPC) 15th World Congress, May 2017, Madrid Spain.