PROTOCOL

HEAD Study

Headache in Emergency Departments

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Statement of Compliance

This study will be conducted in compliance with all stipulation of this protocol, the conditions of the ethics committee approval, the NHMRC National Statement on ethical Conduct in Human Research (2007) and the Note for Guidance on Good Clinical Practice (CPMP/ICH-135/95).

1. SYNOPSIS

Title:	Headache in the Emergency Department: the HEAD study
Short Title:	HEAD
Design:	Prospective multicentre observational study conducted over one calendar month in 2019.
Study Centres:	Emergency Departments in Australia, New Zealand, Hong Kong, Singapore, the United Kingdom, Ireland and Europe
Co-ordinating centre:	Joseph Epstein Centre for Emergency Medicine Research @ Western Health
Study Question:	What is the epidemiology, management and outcome for adult patients treated in the emergency department for headache?
Study Objectives:	**Main Objectives** ➢ To describe the epidemiology of non-trauma related headache in adults presenting to emergency departments including investigations, treatments and outcome **Secondary objectives** ➢ To describe the rate of compliance with recommended practice guidelines for simple headache and migraine. ➢ To describe the rate of compliance with recommended criteria for CT scan in patients with headache ➢ To describe patterns of use of opioid analgesia ➢ To describe the use of codeine-based compounds for the treatment of headache in emergency departments (ED) and ➢ To describe inter-regional variation of investigation and treatment patterns
Inclusion Criteria:	Adult patients (18 or older) with a primary ED presenting problem of headache
Exclusion Criteria:	• History of trauma within 48 hours of presentation • Missing medical records • Inter-hospital transfers • Representation with same headache as previous visit

	• Headache as an associated symptom rather than main complaint
Number of Planned Subjects:	'>1000
Statistical Methods:	Analyses will be descriptive. Binary outcomes will be analyzed using a hierarchical logistical regression model to allow for partial pooling. Partial pooling enables simultaneous estimation of dis-similarity (variation) between centres as well as estimation of the grand mean.

2. GLOSSARY OF ABBREVIATIONS

Abbreviation	Description (using lay language)
ED	Emergency Department
MRI	Magnetic resonance imaging
CT	Computed tomography

3. STUDY SITES

Emergency Departments (ED) in Australia, New Zealand, Asia and Europe. Sites will be recruited by expression of interest. In Australia and New Zealand, all ED accredited for Emergency Medicine training as identified on the Australasian College for Emergency Medicine website will be contacted. In other countries/ regions, hospitals will be approached by local researchers who are members of the steering committee via local networks for Emergency Medicine research. Both public and private hospitals are eligible to participate.

See attachment 1 for a full list of site investigators and sites in Australia.

Expression of interest process for participation is still open.

All participating centres will be provided with a collaboration agreement addressing IP, data security, authorship and publication issues.

4. INTRODUCTION/ BACKGROUND INFORMATION

Headache is a common reason for presentation to emergency departments (ED).[1,2,3]

Headache presentations have been shown to comprise 1.35% (95%CI 1.34-1.36%) of total public hospital ED presentations across Queensland.[4]

There are a wide range of possible causes including:

- Primary headache – benign headache
- Migraine
- Trigeminal neuralgia
- Tumours
- Intracranial haemorrhage including subarachnoid haemorrhage, parenchymal haemorrhage, subdural or extradural haematoma
- Meningitis/ encephalitis/ cerebral abscess
- Toxicities such as carbon monoxide exposure
- Cerebrovascular events

A study from Queensland found that most cases had benign causes and most patients were discharged home.[1] That study looked at investigations and disposition but not at treatments. There is international concern about the use of opioids (especially codeine and pethidine) and their negative health and societal impacts. [5] Headache is one condition implicated in this debate.

The assessment of headache in the ED is complicated by a multiplicity of guidelines and rules. These may be general such as the Australasian College for Emergency Medicine (ACEM) guidelines on diagnostic imaging,[6] the American College of Emergency Physician (ACEP) clinical policy in the evaluation and management of acute headache[7] and the Guidelines in Emergency Medicine Network (GEMNet) UK guidelines for the management of lone acute severe headache.[8] There are also condition specific clinical decision rules such as the Ottawa SAH rule[9,10] and condition specific guidelines e.g. for migraine.[11]

Despite guidelines, there is known variation in practice.[**Error! Bookmark not defined.**,12] That said, whether that variation is at the clinician, hospital or regional level or all of these is not known.

Little is known about the epidemiology of non-trauma related headache in patients attending ED across regional boundaries. Diagnosis, patterns of investigation, treatment and outcome of the patients may vary across regions/ countries.

This study will provide a wider inter-regional and international perspective on the epidemiology of non-trauma-related headache, its investigation, treatment and outcome.

5. STUDY OBJECTIVES

Main Objectives

- To describe the epidemiology of non-trauma related headache in adults presenting to emergency departments including investigations, treatments and outcome

Secondary objectives

- To describe the rate of compliance with recommended practice guidelines for simple headache and migraine.
- To describe the rate of compliance with recommended criteria for CT scan in patients with headache
- To describe patterns of use of opioid analgesia
- To describe the use of codeine-based compounds for the treatment of headache in emergency departments (ED) and
- To describe inter-regional variation of investigation and treatment patterns

6. METHODS

6.1. DESIGN

Prospective multicentre observational study conducted over one calendar month in 2019. Patients will be identified prospectively but, depending on site resources, some data may be collected retrospectively.

6.2. PARTICIPANTS

Inclusion criteria:
Adult patients (aged >18 years) with non-trauma-related headache as their main presenting problem

Exclusion criteria:

- History of trauma within 48 hours of presentation
- Missing medical records
- Inter-hospital transfers
- Representation with same headache as previous visit
- Headache as an associated symptom rather than main complaint

6.3 RECRUITMENT METHODOLOGY

Consecutive adult patients presenting to the ED with non-trauma-related headache as the chief complaint during the study period will be identified from ED data management systems and entered in the study. While patients will be identified prospectively, some data might be collected retrospectively. This will depend on processes and resources at individual sites.

The need for the two approaches to data collection is because many sites will not have the research support infrastructure to collect true prospective data. It is important however to include as many ED as possible to give a more accurate picture of the epidemiology, investigation and treatment. Most of this data should be available in ED information management systems. Sites with research support infrastructure tend to be larger ED with an

academic interest and as such may not be truly representative of the broader ED community. To just include them is likely to be an inaccurate reflection of broader ED practice.

6.4. DATA COLLECTION

Hospitals will be asked to complete an online survey that will include data on annual patient census and availability of CT and MRI scan at their site.

With respect to patient level data, please see attachment 2 for detailed data items and dictionary.

Data will be collected by local researchers onto piloted data forms or directly onto study database (local choice depending on processes/ resources).

It will be entered as **non-identifiable** data to an on-line database (REDCAPS or CASTOR EDC in Europe). The only identifiers will be region and hospital, with the latter used for data verification processes only. Patients will only be identified as case numbers.

JECEMR will provide the necessary tools (data forms) to facilitate control, management and analysis.

JECEMR will manage the REDCAPS database (or CASTOR EDC database in Europe) and provide support for participating sites regarding data entry.

Local data belongs to site investigators who may use it for education, audit and quality assurance purposes.

6.5 ANALYSIS AND SAMPLE SIZE

Data will be analyzed by the coordinating centre. Analyses will be descriptive. Binary outcomes will be analysed using a hierarchical logistical regression model to allow for partial pooling. Partial pooling enables simultaneous estimation of dis-similarity (variation) between centres as well as estimation of the grand mean. This procedure is similar to the random-effects specification in a meta-analysis. Each binary outcome (compliance with guidelines, incidence of CT scans, and prescription of codeine based compounds) will be analysed separately.

No formal sample size calculation is possible as the variation between centres is not known and there are no reliable previously published studies. We have approximately 50 sites across eight countries who have expressed interest in participation which we expect will generate over 1000 patients. If there is no variation between centres, complete pooling is valid and would result in a precision no worse than +- 4%. Without pooling, centre-specific precision will vary between +-4% and +-25%. The centre-specific precision achieved with partial pooling will be improved with partial pooling, however, the relative precision depends on the (unknown) heterogeneity between centres.

6.6. STUDY PERIOD

One month (likely March 2019) for data collection

6.7. MONITOR RESPONSIBLE

Not applicable.

6.8. TREATMENT

Not applicable. No modification to treatment.

6.9. PHASE OF STUDY

Not applicable.

6.10. BIOLOGICAL SAMPLES

Not applicable.

6.11. ADVERSE EVENTS
There is no intervention. No change to usual management is involved.
Adverse events registry and declaration are not applicable.

7. CONSENT

Consent will not be sought at Australian sites as this project will comply with the NHMRC (Australia) negligible risk and waiver of consent guidelines.[13] New Zealand has in the past waived the requirement for consent in similar studies and an application for a similar waiver is being applied for.

The rationale for requesting that the requirement for informed consent be waivered in Australia is based on the NHMRC criteria for such a request.

a. involvement in the research carries no more than low risk.

   This study involves no change to patient care so there are no clinical risks. There is no inconvenience. The only risks involved are related to privacy and confidentiality. There will be mechanisms at the local level to minimize this (separate identifier – case number logs and case report forms without identifiers). All data submitted centrally will be non-identifiable, making this risk negligible.

b. the benefits from the research justify any risks of harm associated with not seeking consent.

As discussed the risks are very low. While there is no direct benefit for participants at the time of the study, there is potential benefit in improved treatment for them and other patients in future.

c. it is impracticable to obtain consent.

Many patients attending ED with headache are experiencing moderate/ severe pain and often unpleasant associated features such as vomiting. Their distress is such that usual consent processes such as reading and signing a PICF is impractical and potentially invalid as their symptoms may distract them from concentrating on its content. Also the process of obtaining consent may cause them distress and confusion by delaying treatment and potentially giving the (false) impression that consent is required for treatment. It is also possible that some patients will have reduced consciousness and will be incompetent to consent. Asking their next of kin for consent could cause them additional anxiety in an already stressful situation and potentially give the (false) impression that consent is required for treatment.

Limiting consent to only those able to participate in a consent process would severely bias our sample towards mild headache and away from the most severe/ serious causes.

d. there is no known or likely reason for thinking that participants would not have consented if they had been asked.

All data is routinely collected (and given by the patient) as part of clinical care. We have no reason to suspect that patients would decline consent.

e. there is sufficient protection of their privacy.

There are data and privacy protections at both local and central levels as described above.

f. there is an adequate plan to protect the confidentiality of data.

This is described above.

g. in case the results have significance for the participants' welfare there is, where practicable, a plan for making information arising from the research available to them (for example, via a disease-specific website or regional news media).

Our results will be presented at conferences and published so that important data, particularly about investigations and treatment is widely disseminated. We anticipate that data about codeine use may be such that a media release will be required for more public dissemination.

In the unlikely event that the data collection process at the local level identifies a risk to an individual patient, such as a missed or misinterpreted investigation result, this will be directed to the site investigator who will manage the issue according to usual quality assurance / clinical follow-up processes which may include informing the patient, arranging further investigations and/or specialist referral. ED routinely check results to identify similar issues, so these processes are already established.

h. There is no possibility of commercial exploitation of derivatives of the study.

i. the waiver is not prohibited by State, federal, or international law.

We will comply with requirements in the various countries involved in the project.

Note, the requirement for ethical approval may vary in different countries and, where required, consent will be obtained according to local practices.

8. PRIVACY AND CONFIDENTIALITY

- Data will be collected by local clinicians who would usually have access to the data as part of clinical care.
- Data entered to the on-line database will be non-identifiable.
- The on-line database will be password secured and stored on the S drive at Western Health.
- Local data collectors will only have access to their own site data.
- Local data will be collected and stored according to local research ethics requirements

9. RISKS AND BENEFITS

There is no direct benefit to participants from their data being included in this study. There is potential for future benefit if the findings are used to promote use of evidence-based therapies and non-use of codeine-based treatments or opioids. This potential benefit also extends to future sufferers of headache treated in ED.

As there is no change to diagnostic processes or treatment, there is no additional clinical risk over standard care. There are small privacy and confidentiality risks which will be mitigated as described above.

In the unlikely event that the data collection process identifies a risk to an individual patient, such as a missed or misinterpreted investigation result, this will be directed to the site investigator who will manage the issue according to usual quality assurance / clinical follow-up processes which may include informing the patient, arranging further investigations and/or specialist referral. ED routinely check results to identify similar issues, so these processes are already established.

9. DATA SECURITY AND HANDLING

Data storage and destruction will comply with ethics standards in each jurisdiction.

In Australia, paper forms (including lists linking study numbers with database case numbers) will be kept in a locked facility (e.g. locked filing cabinet) in a secure defined location (e.g. office of researcher). Databases will be password protected and stored on the S drive at Western Health.

Data will be kept for a minimum of 5 years from date of any publication. After this, paper forms will be destroyed by secure document destruction services used by health services. The database will be destroyed by the data managers.

Processes in other jurisdictions will follow local requirements.

10. DISSEMINATION OF RESULTS

It is our intention that this data will be presented at internal and external educational/ academic meetings and in a publication in a medical journal. In all presentations and publications only non-identifiable, pooled results will be presented.

10.1 Publication rules:

- All publications and presentations must be approved by the HEAD study steering committee.
- Any publication will be communicated to local leads at each participating site.

10.2 Authorship

- The HEAD study steering committee will responsible for the coordination of all articles that will be published.
- The first author will be the one who has made the largest contribution to all aspects of the project, analysis and manuscript preparation.
- Authorship will be decided by members of the HEAD study Steering Committee using ICMJE principles.
- All papers will name the HEAD study group as an author and all site leads will be listed as members of the group in the acknowledgement section.

11. DATA SHARING

On request, each site will be provided with a summary of its own data and be able to compare it with HEAD study pooled data.

Data sharing with other researchers will be considered on a case-by-case basis and subject to additional ethics approval.

12. ATTACHMENTS

Document Name	**Version Number**	**Date (e.g., 18 January 2012)**

Data collection form (with coding)	1	22.08.2018
List of sites expressing interest to participate (Australia)	1	22.08.2018
Site information survey	1	17.09.2018

13. REFERENCES

[1] Chu KH et al. Acute Headache Presentations to the Emergency Department: A Statewide Cross-sectional Study. Acad Emerg Med 2017; 24(1):53-62.

[2] Friedman BW, Serrano D, Reed M, Diamond M, Lipton RB. Use of the emergency department for severe headache. A population-based study. Headache. 2009;49(1):21-30.

[3] Goldstein JN, Camargo CA, Jr., Pelletier AJ, Edlow JA. Headache in United States emergency departments: demographics, work-up and frequency of pathological diagnoses. Cephalalgia 2006;26(6):684-90.

[4] .Chu K, Mahmoud I, Hou XY, Winter C, Jefree R, Brown N, et al. Incidence and outcome of subarachnoid haemorrhage in the general and emergency department populations in Queensland from 2010 to 2014. 2018. Emerg Med Australas. (at press)

[5] Vadivelu N et al. The Opioid Crisis: a Comprehensive Overview. Curr Pain Headache Rep. 2018 Feb 23;22(3):16.

[6] Australasian College for Emergency Medicine. Guidelines on diagnostic imaging. 2012. [February 26, 2018]. Available from: https://www.acem.org.au/getattachment/17ee11f1-bdaf-4ca4-a524-396690123ba7/Diagnostic-Imaging.aspx.

[7] Edlow JA, Panagos PD, Godwin SA, Thomas TL, Decker WW. Clinical policy: critical issues in the evaluation and management of adult patients presenting to the emergency department with acute headache. Ann Emerg Med. 2008;52(4):407-36

[8] Ferguson C. GEMNet Guidelines. Guidelines for the management of lone acute severe headache. 2009.

[9] Perry JJ, Stiell IG, Sivilotti MA, et al. CLinical decision rules to rule out subarachnoid hemorrhage for acute headache. JAMA 2013;310(12):1248-55..

[10] Perry JJ, Sivilotti MLA, Sutherland J, Hohl CM, Emond M, Calder LA, et al. Validation of the Ottawa Subarachnoid Hemorrhage Rule in patients with acute headache. CMAJ. 2017;189(45):E1379-e85.

[11] . Holdgate A, Kelly AM. Emergency Care Evidence in Practice Series, Emergency Care Community of Practice: Migraine in the Emergency Department. National Institute of Clinical Studies [Melbourne, Australia] 2006

[12]Australian Commission on Safety and Quality in Health Care (ACSQHC). Medical Practice Variation: Background Paper. Sydney: ACSQHC, 2013

[13] National Statement on Ethical Conduct in Human Research 2007 (Updated May 2015). Section 2.3.10