Optimal methods for the use of 'pain' as an outcome in systematic reviews of post-operative pain management

CRG Network Lead: **MOSS**

Other CRG Networks involved: **Mental Health and Neuroscience**

Project term:

- Principal investigator: **Christopher Eccleston[1,2];**
- Co Investigators: **Andrew Moore[2] Emma Fisher[1,2], Neil OConnell[2] Nuala Livingstone[3], Anna Erskine[2]**

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Executive Summary

We propose to produce expert guidance on how to manage pain as an outcome in systematic reviews of post-operative care. We focus on a) sources of heterogeneity in methods and reporting, b) the use of primary and secondary endpoints, including surrogate and indirect measures, c) drafting a template and decision-making flowchart, and d) testing that template and flow-chart with different reviews across the network. This work will be driven by PaPaS editors and editorial staff, but involve an invited workshop of experts in the field of post-operative pain for some of the tasks. The final result will be a published article in an open access journal and shared across the networks.

1. Background

Many disease states are characterised by aversive physical sensations only observable by the patient. Pain, fatigue, itch, dizziness, and anxiety, amongst others, have no objectively definable referent and are only available as 'private mental events'. The measurement of private mental events is the cause of much confusion in the fields of clinical trials and evidence synthesis. Some researchers focus on methods of measuring objective correlates of subjective events (physiological or neurological), some focus on attempting to reduce any known biases in the subjective self-report of private events (e.g., psychometrics). Pain is the archetypal private aversive mental sensory experience. What we learn from pain can be used in the study of all of the neglected physical sensations [5]. In post-operative pain, for example, one can measure pain by self-report, clinician report of observed pain behaviour, or a proxy measure such as the timing or extent of requested analgesia. Self-report is the gold standard of pain measurement, and in the pain research and treatment communities the general mantra is: "pain is what the patient says it is". This does not mean that the subjective report of private mental events is not subject to known biases, but it does mean that the primary referent against which other measures are compared is the self-report of pain.

Pain is a common outcome, both primary and secondary, in clinical trials across medicine. The reduced intensity, frequency, or character of pain is often a goal of treatment, or a

welcome consequence [13]. Pain is the main reason people seek help from formal health care; painful conditions include headache, toothache, back pain, arthritis, abdominal pain, other musculoskeletal pain, for example. It is a major reason people prolong a stay in hospital [14]. Acute pain is associated with several very common conditions (dental caries, headache, migraine; [17]). Chronic (longstanding) pain is the major cause of global disability associated with disease [2], and a growing societal problem putting pressure on health care systems as expectations of adequate pain management grow [6; 11].

In Cochrane-PaPaS, we are in the business of synthesizing evidence from clinical trials (and other well conducted studies) for the treatment and management of pain. In this process we have to make numerous decisions about the place of pain and analgesia in both the trials and the reviews. Pain as an outcome is a deceptively simple endpoint. To the lay-person it may seem simple; one wants to reduce pain. There are, however, multiple reasons why the decisions one makes about pain as an outcome are far from simple. Multiple sources of variance in the treatment of pain as an outcome translate into inconsistency and confusion.

Pain is defined as: “distressing experience associated with actual or potential tissue damage with sensory, emotional, cognitive, and social components” [18]. It has sensory qualities (character, temporality, frequency, intensity, novelty, location), affective qualities (fear, motivation, depression), action tendencies (avoidance, escape, or comfort behaviour), and communication properties (sharing the signal of threat). Different aspects are differentially important in different conditions. In headache, for example, the sensory qualities of frequency and intensity are important. In fibromyalgia the affective component is key. And, in low back pain, the action tendencies such as avoidance are more important.

There is no shortage of tools developed to measure pain. They range from the ‘simple’ unidimensional scaled measures of intensity using either a visual or numerical analogue scale (e.g., a 100mm or a 101-point numerical scale anchored with extreme categories (e.g., ‘no pain’ and ‘worst imaginable pain’)) to the multidimensional compound measure trying to capture more than the simple intensity component (e.g., [9; 10]). Even in the unidimensional scaling there is debate over the correct use of anchors [4], whether to use categorical scaling [3], and whether numerical, visual, or other analogues (faces, heat charts, etc.) are optimal [1]. What is clear is that pain must be reported by the patient when this is possible [16].

Further, the deployment of the measurement tool, once decided upon, is also subject to variability. For example, the timing and sampling of measurement are open to much debate: should one measure current pain, pain in the last week, worst pain episode, pain on activity, pain at a particular time such as the night, etc.? This choice is highly influenced by stakeholder preference and engagement. The patient might be interested in the largest reduction in pain (preferably total abolition) on assessment [13], the hospital manager or policy maker might be interested in time to discharge, bed stay, analgesic use [8], the employer might be interested in return to work without further disability [7].

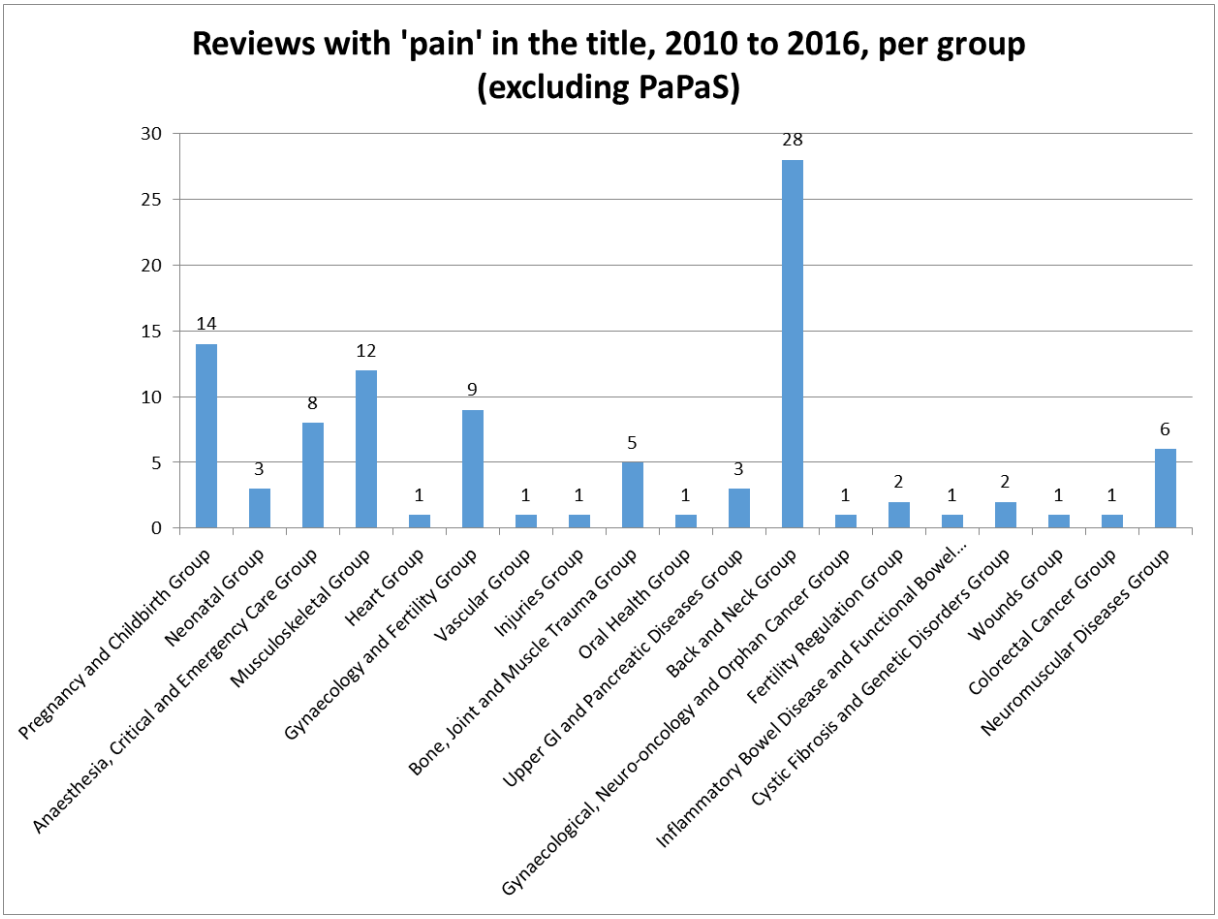
Evidence synthesis requires a series of related protocolised decisions about the appropriate endpoints for use in systematic review with a consideration of a) optimal methods for combining different measurement technologies b) the use of state versus continuous change measures of outcome [12], and c) appropriate and relevant cut-offs for change of status (e.g., moving from moderate pain intensity to a state of no-worse than mild pain or clinically important effects [3; 13]. We will outline how best to present results in summary formats such as GRADE, PLSs, and abstracts, which is critical to consistent and high quality Cochrane Reviews. Within Cochrane there is a tremendous wealth of experience in these matters. In PaPaS we have over 350 reviews with pain as an outcome. We have templates

for reviews investigating either acute or chronic pain, and we have guidance for authors and editors on how to manage pain as an endpoint. Outside of Cochrane there are well-established communities of interest working hard on this problem, in including Standardised Endpoints in Perioperative Medicine (StEP) initiative [15], ACTION (www.action-on-pain.co.uk) and Omeract (www.omeract.org).

2. Purpose

Variability, inconsistency, and error in pain reporting has been identified by Cochrane UK, by the MOSS network, and by other stakeholders. It is an area for which harmonisation and standards will help improve communication, impact, and therefore the reputation of the library.

PaPaS have standards for pain reporting but these are not common within the network or across the Library. In 2017 we asked a then student, Mohammed Abusayed, to undertake a review of how common pain is used as an endpoint in non-PaPaS managed reviews. We did a snapshot review of titles published in the library from 2010 - 2016. After removing PaPaS titles we found 114 titles spread across 19 review groups. See table:



We expect this situation to continue. As I write this, for example, I was notified that 2 titles on pain management for IBD have just been registered with the IBD group.

After consultation within MOSS we decided that providing guidance on all pain outcomes for all pain conditions is too ambitious for this relatively small project, and as a start to focus on pain specific outcomes in a post-operative context.

3. Aim

We aim to provide guidance on the optimal management of pain as an endpoint in systematic reviews including trials of interventions used in a post-operative environment.

4. Objectives

1. To establish a common position on how to conceptualise the measurement of pain as a private mental event subjectively reported by either the patient or an observer.
2. To establish an optimal approach to the use of pain states including change in pain state or a satisfactory state with low or no pain.
3. To provide a framework for dealing with acute postoperative pain for non-pain experts undertaking systematic reviews (in particular Cochrane reviews) where pain following an operation is an outcome.

4.1 Deliverables

1. A published guidance document with decision-making flow chart for use as an addendum for use to any CRG or any author team.

4.2 Proposed methods

A guidance development workshop with experts from the field to discuss minimum and optimal standards of how pain intensity should be extracted from trials and reported within all aspects of Cochrane reviews. This will include reporting standards for the abstract, PLS, results, discussion, SoF tables, and any additional tables.

Task 1: establish the core areas of methodological and interpretative variability in Cochrane reviews which include pain as an outcome. Including consultation with other review group editors who manage pain endpoints.

Task 2: summarise the choices to be made when using pain as an outcome and create flow chart to guide decision-making.

Task 3: establish a template for use in protocols and reviews, for example, a description of the condition (acute postoperative pain), suggested outcomes and measures, as well as minimum standards for reporting in the abstract, plain language summary, and provide guidance on Summary of Findings tables format.

Task 4: independently test the protocol in post-operative pain reviews focussed on pain as an outcome in all eight of the MOSS CRGs.

Task 5: review the template and flow chart following task 4.

Task 6: publish the guidance and decision chart in a primary pain or evidence synthesis outlet with open access.

The PaPaS editorial team will undertake tasks 1 & 2. Task 3, 4 and 5 will be undertaken in a 2-day workshop, held in Oxford or Bath with national and international attendees. Task 6 will be undertaken as with 1&2 but include workshop participants and wider stakeholders from MOSS CRGs.

5. Key milestones and timelines

Management roles: Christopher Eccleston will lead the programme; Anna Erskine will project manage; Nuala Livingstone will facilitate the wider involvement of the members of the networks.

Contributing roles: All other co-investigators will contribute across tasks, in particular in review and facilitating involvement of authors and other experts at the workshop.

	November	December	January	February	March	April	May -
T1: Establish core areas of variability							
T2: flow chart decision making							
T3: draft template for standards							
T4: Test template across reviews							
T5: Review template							
T6: Publish results							

6. Budget

Item 1: Approximately 3 face-to-face meetings with 7 people in Oxford or Bath for UK contributors to manage tasks prior to and after workshop. Average unit cost for travel: £120. 3 meetings x 7 people x £120 = *£2520*

Item 2: Two-day workshop including approximately 12 participants in Oxford or Bath including:

- Travel (£80.00 unit cost) = *£960*,
- 12 nights' accommodation (£150.00 unit cost) = *£1800*,
- Subsistence rates (University of Bath unit costs £50.00 per person per night) = *£1200,*
- Economy air fares for approximately 3 people from US/Canada = *£1200 per person = £3600.*

Overall cost requested <u>£10,000</u>

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F, Gillum RF, Gmel G, Gosselin R, Grainger R, Groeger J, Guillemin F, Gunnell D, Gupta R, Haagsma J, Hagan H, Halasa YA, Hall W, Haring D, Haro JM, Harrison JE, Havmoeller R, Hay RJ, Higashi H, Hill C, Hoen B, Hoffman H, Hotez PJ, Hoy D, Huang JJ, Ibeanusi SE, Jacobsen KH, James SL, Jarvis D, Jasrasaria R, Jayaraman S, Johns N, Jonas JB, Karthikeyan G, Kassebaum N, Kawakami N, Keren A, Khoo JP, King CH, Knowlton LM, Kobusingye O, Koranteng A, Krishnamurthi R, Lalloo R, Laslett LL, Lathlean T, Leasher JL, Lee YY, Leigh J, Lim SS, Limb E, Lin JK, Lipnick M, Lipshultz SE, Liu W, Loane M, Ohno SL, Lyons R, Ma J, Mabweijano J, MacIntyre MF, Malekzadeh R, Mallinger L, Manivannan S, Marcenes W, March L, Margolis DJ, Marks GB, Marks R, Matsumori A, Matzopoulos R, Mayosi BM, McAnulty JH, McDermott MM, McGill N, McGrath J, Medina-Mora ME, Meltzer M, Mensah GA, Merriman TR, Meyer AC, Miglioli V, Miller M, Miller TR, Mitchell PB, Mocumbi AO, Moffitt TE, Mokdad AA, Monasta L, Montico M, Moradi-Lakeh M, Moran A, Morawska L, Mori R, Murdoch ME, Mwaniki MK, Naidoo K, Nair MN, Naldi L, Narayan KM, Nelson PK, Nelson RG, Nevitt MC, Newton CR, Nolte S, Norman P, Norman R, O'Donnell M, O'Hanlon S, Olives C, Omer SB, Ortblad K, Osborne R, Ozgediz D, Page A, Pahari B, Pandian JD, Rivero AP, Patten SB, Pearce N, Padilla RP, Perez-Ruiz F, Perico N, Pesudovs K, Phillips D, Phillips MR, Pierce K, Pion S, Polanczyk GV, Polinder S, Pope CA, Popova S, Porrini E, Pourmalek F, Prince M, Pullan RL, Ramaiah KD, Ranganathan D, Razavi H, Regan M, Rehm JT, Rein DB, Remuzzi G, Richardson K, Rivara FP, Roberts T, Robinson C, De Leòn FR, Ronfani L, Room R, Rosenfeld LC, Rushton L, Sacco RL, Saha S, Sampson U, Sanchez-Riera L, Sanman E, Schwebel DC, Scott JG, Segui-Gomez M, Shahraz S, Shepard DS, Shin H, Shivakoti R, Singh D, Singh GM, Singh JA, Singleton J, Sleet DA, Sliwa K, Smith E, Smith JL, Stapelberg NJ, Steer A, Steiner T, Stolk WA, Stovner LJ, Sudfeld C, Syed S, Tamburlini G, Tavakkoli M, Taylor HR, Taylor JA, Taylor WJ, Thomas B, Thomson WM, Thurston GD, Tleyjeh IM, Tonelli M, Towbin JA, Truelsen T, Tsilimbaris MK, Ubeda C, Undurraga EA, van der Werf MJ, van Os J, Vavilala MS, Venketasubramanian N, Wang M, Wang W, Watt K, Weatherall DJ, Weinstock MA, Weintraub R, Weisskopf MG, Weissman MM, White RA, Whiteford H, Wiersma ST, Wilkinson JD, Williams HC, Williams SR, Witt E, Wolfe F, Woolf AD, Wulf S, Yeh PH, Zaidi AK, Zheng ZJ, Zonies D, Lopez AD, Murray CJ, AlMazroa MA, Memish ZA. Years lived with disability (YLDs) for 1160 sequelae of 289 diseases and injuries 1990-2010: a systematic analysis for the Global Burden of Disease Study 2010. Lancet 2012;380(9859):2163-2196.

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Appendix One: Biographical Sketches and roles

[Principal Investigator] *Christopher Eccleston is Professor of Medical Psychology and Director of the Centre for Pain Research at the University of Bath. He is coordinating editor of the Cochrane Pain, Palliative and Supportive Care (PaPaS) Review Group, Senior Editor for Mental Health and Neuroscience Cochrane Network and Field editor for the Journal, PAIN. He has published approximately 250 papers and 3 books on pain, with a web of science h-index of 69. He is active the areas of: evidence based pain, innovation in pain treatment, digital health, pediatric pain, and the cognitive neurobiology of pain. In 2018 he was awarded the Ronald Melzack Award for Pain Science.*

For 10 recent papers see:

1. Eccleston C, Fisher E, Cooper T, Grégoire MC, Heathcote L, Krane E, Lord S, Sethna N, Anderson A-K, Anderson B, Clinch J, Gray AL, Gold JI, Howard R, Ljungman G, Moore RA, Schecther N, Wiffen P, Wilkinson N, Williams D, Wood C, van Tilburg M, Zernikow B. **Pharmacological interventions for chronic pain in children and adolescents: An overview of systematic reviews**. Pain, in press
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For his recent books see:

1. *Eccleston, C. (2016)* ***Embodied: the psychology of physical sensation****. Oxford University Press, Oxford. ISBN: 9780198727903. e-ISBN: 9780191814099*
2. *Eccleston, C. Wells C, Morlion B (Editors) (2018).* ***European Pain Management.*** *Oxford University Press. ISBN: 9780198785750.*
3. *Wainwright E, Eccleston C (Editors) (2020).* ***Work and pain: a lifespan developmental approach****. Oxford University Press.*

[Co-investigator] *Nuala Livingstone is an Associate Editor supporting the Mental Health and Neuroscience Network, and the Musculoskeletal, Oral, Skin and Sensory (MOSS) Network. After graduating from Queen's University Belfast in 2010 with a PhD in Psychology, Nuala worked as a Research Fellow in the School of Sociology, Social Policy and Social Work at Queen's University Belfast, focusing primarily on authoring and editing Systematic Reviews on topics including Autism, Child Mental Health, Child Maltreatment, Restorative Justice, and Down's Syndrome. In April 2015 Nuala joined the Cochrane Editorial and Methods Department in London as an Editor, working primarily with the Quality Assurance Team. Nuala' s primary job within this team was to conduct pre-publication screening of Cochrane reviews when necessary. Nuala has experience of intervention reviews, diagnostic test accuracy reviews, and network meta-analyses. Nuala's experience to date makes her well suited for the role of co-investigator, as her work with Cochrane have provided her with extensive experience and knowledge of systematic review methodology. In addition, her undergraduate and postgraduate qualifications in psychology also give her good understanding of the sensory qualities, affective qualities, action tendencies and communication properties of the complex outcome of 'Pain'. Some relevant peer-reviewed publications include;*

1. McConachie H, Livingstone N, Morris C, Beresford B, Le Couteur A, Gringras P, Garland D, Jones G, Macdonald G, Williams K, Parr JR. (2018) **Parents Suggest Which Indicators of Progress and Outcomes Should be Measured in Young Children with Autism Spectrum Disorder.** J Autism Dev Disord. Apr;48(4):1041-1051. doi: 10.1007/s10803-017-3282-2
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[Co-investigator] *Andrew Moore is an Oxford trained Biochemist (MA, DPhil, DSc) who has been researching pain since the late 1970s. This involved the development of sensitive measuring systems for opioids in body fluids, the pharmacokinetics and pharmacodynamics of opioids by different routes of administration, and investigating and understanding morphine metabolism in man. More recently he has been involved with clinical trial design, and particularly the design and understanding of pain Trials. Andrew was involved with the (pre-Cochrane) development of evidence-based methods in pain, and has had a particular interest in understanding factors contributing to major bias in pain (and other) trials, including effects of study size and imputation methods. He is an honorary fellow of the Royal College of Anaesthetists, and an honorary member of the International and British pain societies. He has published over 600 papers (predominantly on pain) and several books on pain, with a web of science h-index of over 80. Relevant publications include:*

1. Moore RA, Derry S, Wiffen PJ, Banerjee S, Karan R, Glimm E, Wiksten A, Aldington D, Eccleston C. **Estimating relative efficacy in acute postoperative pain: network meta-analysis is consistent with indirect comparison to placebo alone.** Pain. 2018;159:2234-2244.
2. Häuser W, Finnerup NB, Moore RA. **Systematic reviews with meta-analysis on cannabis-based medicines for chronic pain: a methodological and political minefield**. Pain. 2018;159:1906-1907.
3. Seers T, Derry S, Seers K, Moore RA. **Professionals underestimate patients' pain: a comprehensive review.** Pain. 2018 May;159(5):811-818.
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5. Geneen LJ, Moore RA, Clarke C, Martin D, Colvin LA, Smith BH. **Physical activity and exercise for chronic pain in adults: an overview of Cochrane Reviews.** Cochrane Database Syst Rev. 2017 Apr 24;4:CD011279.
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1. Eccleston C, Fisher E, Cooper T, Grégoire MC, Heathcote L, Krane E, Lord S, Sethna N, Anderson A-K, Anderson B, Clinch J, Gray AL, Gold JI, Howard R, Ljungman G, Moore RA, Schecther N, Wiffen P, Wilkinson N, Williams D, Wood C, van Tilburg M, Zernikow B. **Pharmacological interventions for chronic pain in children and adolescents: An overview of systematic reviews**. Pain, in press
2. Law, E. F., Fisher, E., Eccleston, C., & Palermo, T. M. (2019). **Psychological therapies for parents of children and adolescents with chronic illness.** *Cochrane Database of Systematic Reviews,* Issue 3. Art. No: CD009660. DOI: 10.1002/14651858.CD009660.pub4.
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[Co-investigator] *Neil O'Connell is a Senior Lecturer in Physiotherapy in Brunel University in the UK. He is a member of the editorial board of Cochrane's Pain, Palliative, and Supportive Care (PaPaS) group and the Journal of Pain and is the senior commissioning editor for the pain science blog Body in Mind (www.bodyinmind.org). Neil was a member of the Guideline Development Group for the UK's National Institute of Health and Care Excellence (NICE) 2016 guideline for the management of low back pain and sciatica and contributed to the NICE Quality Standard on that topic. He is currently a NICE expert advisor, He has published approximately 60 papers, including numerous Cochrane reviews and currently has a Scopus h-Index of 20.*

For 10 recent papers see:

1. Gibson W, Wand BM, Meads C, Catley MJ, O'Connell NE **Transcutaneous electrical nerve stimulation (TENS) for chronic pain - an overview of Cochrane Reviews** Cochrane Database Systematic Reviews. 2019;4:CD011890
2. Smith KJ, Peterson MD, O'Connell NE, Victor C, Liverani S, Anokye N, Ryan JM. **Risk of depression and anxiety in adults with cerebral palsy**. JAMA Neurology Published ahead of print.
3. O'Connell NE, Marston L, Spencer S, DeSouza LH, Wand BM. **Non-invasive brain stimulation techniques for chronic pain**. Cochrane Database of Systematic Reviews 2018, Issue 3. Art. No.: CD008208. DOI: 10.1002/14651858.CD008208.pub4. (listen to the podcast https://www.cochrane.org/podcasts/10.1002/14651858.CD008208.pub5)
4. Wei-Ju Chang, Neil E O'Connell, Paula R Beckenkamp, Ghufran Alhassani, Matthew B Liston, Siobhan M Schabrun. **Altered Primary Motor Cortex Structure, Organisation and Function in Chronic Pain: A Systematic Review and Meta-Analysis**. Journal of Pain 2018; 19(4):341-359.
5. Gibson W, Wand BM, O'Connell NE. **Transcutaneous electrical nerve stimulation (TENS) for neuropathic pain in adults.** Cochrane Database of Systematic Reviews 2017; 9:CD011976.
6. Gittings P, Gisbrook T, Edgar DW, Wood FM, Wand BM, O'Connell NE. **Resistance Training for Rehabilitation after Burn Injury: A Systematic Literature Review & Meta-Analysis**. Burns 44(4):731-751
7. Ryan JM, Cassidy EE, Noorduyn SG, O'Connell NE**. Exercise interventions for cerebral palsy.** Cochrane Database of Systematic Reviews 2017, Issue 6: CD011660.
8. O'Connell NE, Cook C, Wand BM, Ward SP. **Clinical guidelines for low back pain. A critical review of consensus and inconsistencies across three major guidelines**. Best Practice & Research Clinical Rheumatology 2016; 30(6):968-980
9. O'Connell NE, Kamper SJ, Stevens M, Lee Q. **Twin peaks? No evidence of bimodal distribution of outcomes in clinical trials of non-surgical interventions for spinal pain: An exploratory analysis.** J Pain 2017; 18:8: 964-972.
10. O'Connell NE, Wand BM, Gibson W, Carr DB, Birklein F, Stanton TR. **Local anaesthetic sympathetic blockade for complex regional pain syndrome**. Cochrane Database Syst Rev.2016 Jul 28;7:CD004598

[Co-investigator] *Anna Erskine is the Managing Editor (ME) for the PaPaS CRG (since 2012). She supports the development and publication of PaPaS reviews in the Cochrane Library, and manages a portfolio of over 300 titles. Anna was involved in an NIHR Programme Grant (2014-17) to produce more than 50 reviews addressing the unmet need of chronic pain, which involved the development and management of template protocols.*

She has developed guidance documents for protocols, reviews and updates, for use by author teams and editors; the documents include suggested standardized text, mandatory MECIR standards, and key information from the Handbook, Style Manual, and Cochrane policies. These documents are freely available, and are updated as necessary. Anna regularly facilitates and contributes to meetings, workshops and events. Anna is managing the recruitment of, and will be direct Line Manager to, two Network Support Fellows, including the NSF for the MOSS Network.

Panel Review and response to review

From: Chris Eccleston <hssce@bath.ac.uk>
Date: Wednesday, 22 May 2019 at 20:02
To: Tarang Sharma <tsharma@cochrane.org>
Cc: Nuala Livingstone <nlivingstone@cochrane.org>, Karla Soares-Weiser <ksoares-weiser@cochrane.org>
Subject: CRG Networks Innovation Fund 2019

Dear Taranga

Thank you for your email and the excellent news that the Innovation Fund proposal for the MOSS network was received favourably. In response to the three queries

1. We are pleased that the committee recognised the importance of the problem, in relation to the comment "*Pain is a common and important outcome which is currently inconsistently evaluated across reviews*". We also stressed in the proposal that our learnings from this project could extend beyond pain to similar standardisation work in which the self-report of private mental events (such as physical sensations) are the outcomes of interest.

   It is true that trialists often report different pain outcomes. Sometimes this is driven by a professional community agreement (e.g., headache) by stakeholder prioritisation (e.g., palliative care) or by over-comprehensiveness (lumping). In PaPaS we recognise the large number of possible endpoints and scales. We have developed ways to measure pain intensity differences and total pain relief, for example, regardless of scale, and across outcomes. We know that pain relief has an inverted distribution (U shaped) which means it is often bimodal, so approaches to data transformation, avoidance of mean data, and a focus on responders may be needed. Similarly, the timing of effects can cause major problems in data analyses. In some initially painful conditions, pain can wane rapidly, making longer duration studies of dubious relevance.

   In essence, we tried (and perhaps failed for some of the panel) to communicate that pain can appear to be a simple outcome, and is often used in general methods discussions as simple. But in fact it is very complex. Different trials choose different aspects of pain measured in various ways. But there are well-researched methods of managing this heterogeneity that are used commonly in reviews edited in PaPaS, MSK, and NMD, and incorporated into different templates. These groups have guidance based on the current evidence in research synthesis and pain measurement. However, they are rarely used by other CRGs. As we have shown, this is a prevalent problem across the library.

2. The panel had the comment: "*It's not completely clear to me how this proposal will lead to improved choice of pain outcomes. For example, task 2 is to summarise the choices made when using pain as an outcome and create a flow chart to guide decision making. But, it's not clear how the applicants' research will underpin the decision making guide*". That is helpful. We did give details on the exact process as we were concerned to describe the

methods that included Cochrane stakeholders so they different common PICOs could be captured. In this process we do want representatives from other MOSS groups to be represented. For examples pain secondary to itch in skin disorders, or primary dental pain, may want to make a specific case for how they differ compared with post-operative pain or cancer pain. But we can give some examples of the types of issues we often deal with which can lead to an improved choice of patient pain outcome. For a first example a guideline might ask reviews to consider whether initial pain (pain on study entry) was of sufficient intensity to allow for any sensitive analgesic result to be obtained. It may be surprising to learn that many are not, and knowing this alone is an aid to interpretation. For a second related example, knowing that a visual analogue scale of pain intensity score of 20/100 is only mild pain (and given this value by patients) allows a different judgement to be made about a reduction to 10/100. It may be a 50% reduction in pain intensity, but that's very different from a pain intensity of 90 and 45. That's also a 50% reduction, but in the first case both scores are acceptable, while in the latter neither is. Signposting to reviewers and editors to address these scaling issues will help. I could go on but will resist. What seems like a simple outcome is very complex and involves a series of judgements that influence the analysis and the interpretation.

3. The panel had the comment: "*systematic review authors often have little choice in the pain measures they include, since these are determined by the trialists. So, it's not clear to me that the proposal will bring about important improvements*." We agree with the first part of this statement. This is the point really. But in reality trialists often report multiple outcomes in the trial and study report. We would encourage fore-thought and expert deliberation as to the most appropriate outcome to be used at the protocol stage (before seeing the published report or the clinical trial report). There is a lot of poor practice in reviews on the library which unthinkingly accept the outcomes 'picked' by trialists (not always in their protocols) and which are often phrased in ways that are not clinically neutral. A good example is the common us of 'mean change in analgesic consumption' as a secondary and sometimes primary outcome. This often equated with mg morphine equivalents. This is a highly skewed outcome, driven by a very few high usage participants. In this case a flow chart would help authors to downgrade a few mg change in morphine, and alternately use another, more clinically relevant measure, or one more directly important to people with pain. These are examples of cases in which important improvements can be achieved.

Finally, we have reconsidered the budget and are confident that we can deliver the work within the £10,000 budget. We can scale the work to meet the funding. Also, alternatively, we will explore how a successful award can allow us to leverage further funding, either from individuals who when invited to contribute can cover their costs locally, or from support from the International Association for the Study of Pain, Special Interest Group in Methods, Evidence and Research Synthesis who are equally interested in this area. We will, of course, follow the Cochrane Commercial Conflict of Interest Policy.

I trust this is a satisfactory response to the questions raised. If I can help further, please do not hesitate to contact me.

Kind regards

Chris

Christopher Eccleston
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Director, Centre for Pain Research, &
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