Reproducible and replicable pain research: a critical review

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1. INTRODUCTION

Recently, the degree to which scientific publications provides a reliable source of information has come under intense scrutiny. Reports suggest that a substantial amount of published literature is likely to be biased [28], distorted [27,53], and non-reproducible [7,50]. This cuts across basic [10,55], pre-clinical [1,16], and clinical research [4,50]. It has been estimated that non-reproducible preclinical research consumes $28 billion/year (USD) [16] and that 85% of biomedical research resources are wasted on biased research [35].

The response from the scientific and policy community has been to identify common practices that contribute to the problem, and develop methods to counteract them [47]. This matter is very relevant to the pain field [1]. Understanding the causes of non-reproducible and non-replicable research and its ultimate impact on how we prevent and treat pain should assist pain researchers to improve the reproducibility and replicability of their work. The distinction between reproducibility and replicability is presented in **Figure 1** and defined elsewhere [51]. This paper aims to: (1) define drivers of non-reproducible and non-replicable research with examples from pain sciences and broader research fields; and (2) provide an overview of potential solutions and practices that could improve reproducibility and replicability of pain research.

2. FACTORS DRIVING NON-REPRODUCIBLE AND NON-REPLICABLE RESEARCH

2.1 Transparency of research reports

Perhaps the biggest barrier to both reproducibility and replicability is a lack of transparency in reporting. Research reports should include complete and accurate documentation of research intent, research processes, research outcomes, and implementation. Opaque reporting practices include not reporting on entire studies [24], selective reporting (or non-

reporting) of study outcomes [19], incomplete reporting of methods or incomplete description of interventions [18,22], and inaccurate or misleading reporting of results and inferences [8,34]. Opaque reporting makes reproducing a study difficult and can make replicating it impossible [26,77].

This lack of transparency appears to be common in the pain field, affecting aspects of study design, intervention, and outcome reporting. For example: of 172 reports of randomised trials evaluating analgesic interventions, only 38% provided sufficient information to replicate a sample size calculation [38]; of 38 exercise trials for patellofemoral pain, none reported complete information about the intervention according to the TIDierR reporting guideline and only 8% reported on intervention fidelity and adherence [23]. Likewise, for outcome reporting, a review of 262 studies showed that reports often lacked important detail about pain intensity assessments, frequency and type of assessments, and pain location [69]. Selective publication of positive trial findings has also been identified as a pertinent issue in the pain field [62].

2.2 Underpowered studies

Underpowered studies have insufficient participants, subjects or data points to make robust estimates of effects. This may result in spurious (false-negative or false-positive) findings [12,42], effects of greater magnitude than the real population effect, and estimates with low precision [10,56]. Across multiple disciplines, primary studies confer less than 50% power to detect true effects [10,13]. In neuroimaging studies, the median power has been estimated to be around 8% [10]; in rheumatoid arthritis studies - 19% [13]. In the psychology literature, recent attempts to replicate findings have shown that, when replication studies are sufficiently powered, the effect size is on average half that of the original study [50]. Presumably the

same problem applies to underpowered studies in our field, a situation probably compounded by the common absence of sample size calculations in pain research reports [38]. These issues are of critical importance because underpowered studies may misinform clinical practice and policy through misrepresentation of effects.

2.3 Researcher degrees of freedom

The term 'researcher degrees of freedom' refers to the decisions made by a researcher from project conception to dissemination, all of which may shift the outcome and impact of the project, usually towards false positive discoveries [10]. A survey of brain stimulation researchers suggested that 30% reject outliers without a statistical rationale, 30% exclude data after looking at the results, and 38% clean data points based on 'gut feeling'[21]. Common analytical decisions, such as dropping an experimental group from the analysis (e.g. failed experimental manipulations), have been shown to inflate the nominal 5% chance of a false positive finding [67]. This problem has been recognised and partly attributed to the inordinate and longstanding pressure to publish, although we can only speculate on the extent to which decisions made to improve the chances of interesting findings are wilful [14,15,57].

2.4 The wider context

There are inherent personal and institutional incentives that propagate the fundamental problems identified above [14] – we are sympathetic to the cultural forces at play [45,46]. Smaldino and McElreath (2016) showed that current academic incentives, such as being rewarded for large publication volume, high citation rates, and grant success, increase the risk of poor research methodology [68]. They posit a Darwinian perspective: that there is 'natural variation' in the quality of research practices, and that in a competitive environment - the practices and habits that lead to reward (publication, grant success, tenure, promotion, grants,

prestige) are selected and passed from advisors to trainees, and across peers [68]. The 'surviving' practices may lead to high output volume – itself associated with high rates of false-positive discoveries [28,67] - but not necessarily to approximating the truth. These pressures clearly affect our community [46] and contend that the field can benefit from improving standards for transparency.

3. POTENTIAL SOLUTIONS & RECOMMENDATIONS

3.1 Pre-registration

Pre-registration is the practice of making a public, time-stamped record of the research plan, before data collection commences [9,40]. Pre-registration provides a strong incentive to plan and execute best scientific practice and protects against selective reporting, p-hacking, and spin [47,74]. It allows the consumer of the research to know, for example, when a study intended to test multiple (exploratory) hypotheses, yet reported only the favourable result; or intended to explore a single hypothesis using several model specifications, yet only reported the model that yielded a favourable result. Pre-registration does not necessarily prevent all threats to validity, however it does stimulate transparency by encouraging researchers to explain deviations in the research process.

Pre-registration is considered standard practice for randomised controlled trials and systematic reviews. Seven of the 10 leading journals in our field specify that pre-registration is required for clinical trials; one encourages it for systematic reviews, and none require nor encourage it for observational or experimental studies (**Table 1**). This shows that pre-registration is not considered standard practice for systematic reviews, observational studies and pre-clinical studies in our field. Given the advantages of pre-registration observed in clinical trials [2,3], it is possible that the benefits may outweigh those costs. However, to do

so is not without substantial challenges that will require innovative solutions. Mogil and Macleod (2017) have proposed a model whereby exploratory studies deposited in preprint servers are followed up by a 'preclinical trial' with higher standards of rigour [41]. It would seem timely that we determine the value and impact of such approaches.

Outside our field, incentives are already in place to expand pre-registration practices beyond clinical trials and systematic reviews. For example, the Centre for Open Science introduced a US$1M funding incentive that rewards investigators for publishing research that was pre-registered via the Open Science Framework. Our leading institutions, for example the International Association for the Study of Pain, could take a leadership role here. For example, pre-registration could be weighted in the evaluation of abstracts submitted to conferences, in the consideration of scholarship, prize and grant applicants. Similar incentives could be proposed by pain journals, for example: including a question about pre-registration on manuscript submission platforms, and encouraging the use of pre-registration facilities such as the Open Science Framework. Unfortunately, passive implementation of pre-registration facilities has shown limited effect in reducing discrepancies between pre-registration and published reports [70]. Active monitoring by investigators and peer reviewers might be required to ensure that discrepancies are minimised, or at least, transparently reported. This could be achieved at manuscript level by a requirement to include the subheading 'deviations from protocol' or similar in the methods section.

Anecdotally, some researchers are reluctant to pre-register their research for fear of having their ideas scooped. However, pre-registration can remain hidden from public view for a pre-determined embargo period, which protects researchers from scooping (and from being accused of scooping), because it provides irrefutable evidence of the time a project was

started. Some might also suggest that pre-registration will penalise discovery and stifle innovation. We do not think this is necessarily the case - plans can change for important and innocent reasons; such as a serendipitous finding, a loss of funding or poor recruitment. Pre-registration merely obliges the researcher to report the reason for the change; it is not a punitive measure.

3.2 Registered reports

Registered reports provide similar information to pre-registration documents but are also peer reviewed based on method. They offer 'in-principle' acceptance at first peer review, and if the second peer review (at study completion) verifies that the study complied with the registered report and the interpretation is valid, the paper is accepted [11,49]. Registered reports are an advance on pre-registration because they mandate publication irrespective of the results, which reduces the risk of selective publication [49]. Registered reports and pre-registration do not impede exploratory research, but they facilitate the distinction between exploratory and confirmatory research up front by giving researchers the opportunity to declare the nature of the work [49].

As of November 2017, the Centre for Open Science indicated that 80 journals across all scientific disciplines accepted registered reports [73]. Some of these journals, for example *Cortex* [11], *Behavioural Neuroscience* [60], *BMC Medicine* [73], *BMC Biology* [60], are relevant to the pain field and publish pain-related research (e.g. [29,58]). At the time of writing, no mainstay pain journals offered publication of registered reports (**Table 1**). This seems to present an excellent opportunity to move our field forward.

3.3 Sharing code, data, and reproducible workflow

Sharing data and statistical code advances transparency by enabling external scrutiny. Modern statistical software such as *SPSS [IBM Corp: Armonk, NY, USA]*, *SAS [SAS Institute Inc: Cary, NC, USA]*, *STATA [StataCorp LLC: College Station, TX, USA]*, *MATLAB [The Mathworks Inc: Natic, MA, USA]*, and *R [R Foundation for Statistical Computing: Vienna, Austria]* allow researchers to save the code document that was used to analyse the data. These code documents, along with links to de-identified data sets, are being shared via journal websites, and some journals are now recommending this practice [20]. To fully enable reproducibility [52], researchers may need to also provide accompanying scripts that describe how the code was applied to the data. This has become possible via "literate programming" [52], which allows the investigator to combine data, code, output, and the narrative text into a single reproducible document [54]. Modern tools that can produce these documents include *knitr* (R Markdown) [76] and *Jupyter Notebooks* [33].

The value and ethical obligations of sharing raw data is well accepted by funders, journals, researchers, and consumers [32,71]. Accordingly, the International Committee of Medical Journal Editors (ICMJE) recently mandated the inclusion of data sharing agreement statements within clinical trials reports submitted to ICMJE journals [72]. Pain researchers could adhere to this practice by clearly stating in their protocols whether, with whom and how, de-identified data will be made available. At present, there is no mandate for pre-clinical and observational studies, and it remains uncommon practice [36,37]. The FAIR principles for data sharing might help pain researchers share data that are findable, accessible, interoperable, and re-usable [75]. Although these steps would bring clear benefits, they would also require safeguarding of patient and participant privacy [5,71] and bring other challenges, the solutions to which are not currently obvious.

Although some may be reluctant to embrace data sharing until all risks are averted, there is already movement towards data-sharing. Meetings such as the Data Sharing Summit have gathered and attempted to reconcile the views of representative group leaders [61], and more recently, funders such as the Wellcome Trust, The Bill & Melinda Gates Foundation, Cancer Research UK and the UK Medical Research Council have engaged with ClincalStudyDataRequest.com to streamline data sharing mechanisms [65]. New journal outlets for data [63] and novel approaches to data authorship [6] have been advocated to incentivise data sharing. However, until funders and academic organisations acknowledge these practices with credit, the pursuit to open data could remain stagnant. In our field, five of the 10 leading journals engage with data sharing. Two of these journals require, and the other 3 encourage data sharing statements in the manuscript. Four of the 10 leading journals encourage sharing code but none mandate it (**Table 1**).

3.4 Reporting guidelines

Reporting guidelines advise on the minimum information that is required for a transparent account of research methods and findings. These guidelines usually involve a checklist, flow diagram or set of instructions that relate to a specific type of research [43]. Adherence to reporting guidelines can prevent study details from being misrepresented when they are used in systematic reviews, clinical practice and policy. It also reduces the likelihood of research waste, and increases the utility and likely implementation of research findings [66]. As of November 2017, the Enhancing the QUAlity and Transparency Of health Research (EQUATOR) network [66] maintains a searchable database of 386 reporting guidelines. Researchers can consult the EQUATOR network for relevant guidelines and use the decision aid (https://www.penelope.ai/equator-wizard) to select appropriate guidelines for major study types [64].

Recent evidence suggests that active implementation of these guidelines may be needed, beyond the near-standard endorsement from ICMJE journals, to ensure sufficient reporting. Hopewell et al. [25] have shown that active implementation of the CONSORT for Abstracts reporting guideline (i.e. by emailing authors to revise the submitted abstracts according to the guidelines, or changes made by journal editors during peer review) was associated with a 53% improvement in reporting quality. Although promising, it is not yet known whether these findings generalise across other reporting guidelines. It will be important to gauge the effect of the recent pain-specific supplement to the Consolidated Standard of Reporting Trials (CONSORT) statement [17] and the ARRIVE guidelines [59]. In our field, four of the 10 leading journals require the submission of core reporting guidelines such as the CONSORT statement, and three encourage their use (**Table 1).**

4. FUTURE DIRECTIONS

We have suggested several strategies by which the pain field can continue to strive towards greater transparency in scientific practice and indeed, take a leadership role. We used evidence generated within the pain field and meta-research from general disciplines to highlight the causes and consequences of non-reproducible and non-replicable research. Our snapshot of current policies of pain journals (**Table 1**) should not be interpreted to reflect the overall quality of the journals, but as a platform from which to engage with the challenges researchers face and to guide future changes in journal policy for better transparency – as reflected by Keefe et al. [30]. Indeed, the overall prevalence and implications of research transparency within the pain field remains to be determined. As such, meta-research, bibliographic studies, and original research to identify specific practices and cultures that

impose threats to reproducible and replicable pain science would seem warranted. There is also a need to evaluate the impact of recommended practices on outcomes that gauge reproducibility and biases. Robust findings from such studies could inform strategies to modify pain researchers' behaviours and change journal policies and funding rules.

That academic-reward and publishing systems that incentivise scientific practice need to change has been well recognised and changes can be made at all levels; as funders, journals, reviewers, researchers, and consumers [47]. Some are relatively straightforward changes, for example journals educating readers on the pertinent issues, 'badging' papers with optimal transparency [31], publishing registered reports, and mandating pre-registration for all study designs. Other strategies include individual signatories to the Peer Reviewer's Openness Initiative [44] declining to review papers that do not meet minimum standards of transparency at time of submission; special calls for replication papers, or funding for large-scale replication studies in the pain field. Recognition of these practices within institutions and funding schemes would send a clear message that transparent scientific practice is worthwhile and not counter-productive to career prospects [39]. Finally, we contend that pain journals should sign the Transparency and Openness Promotion (TOP) Guidelines [48] - a set of standards intended to assist journals steward transparent scientific practices. Currently, only three of the 10 leading pain journals are TOP signatories.

5. Summary

That much research may be biased, distorted or untrue has clear implications for the pain field. There are profound ethical and economic reasons for pursuing research practices that promote reproducibility and replicability of pain studies. A cultural shift toward openness and transparency in science is well underway but is not without its challenges. We suspect that

collaboration between pain researchers, journals, funders and institutions will be required to generate, adopt, and promote open science principles, and thereby accelerate progress in our field. In so doing, we can only improve outcomes for people in pain.

CONFLICTS OF INTEREST

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REFERENCES

[1] Andrews NA, Latremoliere A, Basbaum AI, Mogil JS, Porreca F, Rice ASC, Woolf CJ, Currie GL, Dworkin RH, Eisenach JC, Evans S, Gewandter JS, Gover TD, Handwerker H, Huang W, Iyengar S, Jensen MP, Kennedy JD, Lee N, Levine J, Lidster K, Machin I, McDermott MP, McMahon SB, Price TJ, Ross SE, Scherrer G, Seal RP, Sena ES, Silva E, Stone L, Svensson CI, Turk DC, Whiteside G. Ensuring transparency and minimization of methodologic bias in preclinical pain research: PPRECISE considerations. Pain 2016;157:901–909.

[2] Antes G. Registering clinical trials is necessary for ethical, scientific and economic reasons. Bull World Health Organ 2004;82:321.

[3] Antes G, Dickersin K. Trial registration to prevent duplicate publication. Jama 2004;291:2432.

[4] Azad TD, Veeravagu A, Mittal V, Esparza R, Johnson E, Ioannidis J, Grant GA. Neurosurgical Randomized Controlled Trials—Distance Travelled. Neurosurgery 2017; June (online first).

[5] Bauchner H, Golub RM, Fontanarosa PB. Data Sharing An Ethical and Scientific Imperative. Jama 2016;315:1237–1239.

[6] Bierer BE, Crosas M, Pierce HH. Data Authorship as an Incentive to Data Sharing. N Engl J Med 2017;376:1684–1687.

[7] Boekel W, Wagenmakers EJ, Belay L, Verhagen J, Brown S, Forstmann BU. A purely confirmatory replication study of structural brain-behavior correlations. Cortex 2015;66:115–133.

[8] Boutron I, Altman DG, Hopewell S, Vera-Badillo F, Tannock I, Ravaud P. Impact of spin in the abstracts of articles reporting results of randomized controlled trials in the field of cancer: the SPIIN randomized controlled trial. J Clin Oncol 2014;32:4120–4126.

[9] Buck S. Solving reproducibility. Science 2015;348:1403.

[10] Button KS, Ioannidis JP, Mokrysz C, Nosek B, Flint J, Robinson ESJ, Munafò MR. Power failure: why small sample size undermines the reliability of neuroscience. Nat Rev Neurosci 2013;14:365–76.

[11] Chambers CD, Dienes Z, McIntosh RD, Rotshtein P, Willmes K. Registered reports: realigning incentives in scientific publishing. Cortex 2015;66:A1–A2.

[12] Cohen J. Statistical power analysis. Curr Dir Psychol Sci 1992;1:98–101.

[13] Dumas-mallet E, Button KS, Boraud T, Gonon F, Munafò MR. Low statistical power in biomedical science: a review of three human research domains. R Soc Open Sci 2017;4:160254.

[14] Edwards MA, Roy S. Academic Research in the 21st Century: Maintaining Scientific Integrity in a Climate of Perverse Incentives and Hypercompetition. Environ Eng Sci 2017;34:51–61.

[15] Fanelli D. Do pressures to publish increase scientists' bias? An empirical support from US states data. PLoS One 2010;5:e10271.

[16] Freedman LP, Cockburn IM, Simcoe TS. The economics of reproducibility in preclinical research. PLoS Biol 2015;13:e1002165.

[17] Gewandter JS, Eisenach JC, Gross RA, Jensen MP, Keefe FJ, Lee DA, Turk DC. Checklist for the preparation and review of pain clinical trial publications. PAIN Reports 2017;0:1.

[18] Glasziou P, Meats E, Heneghan C, Shepperd S. What is missing from descriptions of treatment in trials and reviews? Bmj 2008;336:1472.

[19] Goldacre B, Drysdale H, Powell-Smith A, Dale A, Milosevic I, Slade E, Hartley P, Marston C, Mahtani K, Heneghan C. The COMPare Trials Project. 2016. Available: www.COMPare-trials.org. Accessed 8 Feb 2018.

[20] Herbert R, Elkins M. Publishing code: an initiative to enhance transparency of data analyses reported in Journal of Physiotherapy. J Physiother 2017;63:129–130.

[21] Héroux ME, Taylor JL, Gandevia SC. The Use and Abuse of Transcranial Magnetic Stimulation to Modulate Corticospinal Excitability in Humans. PLoS One 2015;10:e0144151.

[22] Hoffmann TC, Glasziou PP, Boutron I, Milne R, Perera R, Moher D, Altman DG, Barbour V, Macdonald H, Johnston M, Lamb SE, Dixon-Woods M, McCulloch P, Wyatt JC, Chan A-W, Michie S. Better reporting of interventions: template for intervention description and replication (TIDieR) checklist and guide. Bmj 2014;348:g1687.

[23] Holden S, Rathleff MS, Jensen MB, Barton CJ. How can we implement exercise therapy for patellofemoral pain if we don't know what was prescribed? A systematic review. Br J Sports Med 2018;52:385.

[24] Hopewell S, Loudon K, Clarke MJ, Oxman AD, Dickersin K. Publication bias in clinical trials due to statistical significance or direction of trial results. Cochrane Database Syst Rev 2009;21:MR000006.

[25] Hopewell S, Ravaud P, Baron G, Boutron I. Effect of editors' implementation of CONSORT guidelines on the reporting of abstracts in high impact medical journals: interrupted time series analysis. Bmj 2012;344:1–7.

[26] Ioannidis JPA. Adverse events in randomized trials: neglected, restricted, distorted, and silenced. Arch Intern Med 2009;169:1737–1739.

[27] Ioannidis JPA. Excess Significance Bias in the Literature on Brain Volume Abnormalities. Arch Gen Psychiatry 2011;68:773.

[28] Ioannidis JPA. Why most published research findings are false. PLoS Med 2005;2:e124.

[29] Karran EL, McAuley JH, Traeger AC, Hillier SL, Grabherr L, Russek LN, Moseley GL. Can screening instruments accurately determine poor outcome risk in adults with recent onset low back pain? A systematic review and meta-analysis. BMC Med 2017;15:13.

[30] Keefe FJ, Ballantyne J, Blyth F, Coghill RC, Dickenson A, Dionne CE, Eccleston C, Finnerup NB, Kuner R, Seminowicz DA, Sluka K. Publishing the best basic and applied pain science: open science and PAIN. Pain 2018;159:405–406.

[31] Kidwell MC, Lazarević LB, Baranski E, Hardwicke TE, Piechowski S, Falkenberg LS, Kennett C, Slowik A, Sonnleitner C, Hess-Holden C, Errington TM, Fiedler S, Nosek BA. Badges to Acknowledge Open Practices: A Simple, Low-Cost, Effective Method for Increasing Transparency. PLoS Biol 2016;14:1–15.

[32] Kiley R, Peatfield T, Hansen J, Reddington F. Data Sharing from Clinical Trials — A Research Funder's Perspective. N Engl J Med 2017;377:1990–1992.

[33] Kluyver T, Ragan-Kelley B, Pérez F, Granger BE, Bussonnier M, Frederic J, Kelley K,

Hamrick JB, Grout J, Corlay S. Jupyter Notebooks-a publishing format for reproducible computational workflows. Positioning and Power in Academic Publishing: Players, Agents and Agendas.2016. pp. 87–90.

[34] Lazarus C, Haneef R, Ravaud P, Boutron I. Classification and prevalence of spin in abstracts of non-randomized studies evaluating an intervention. BMC Med Res Methodol 2015;15:85.

[35] Macleod MR, Michie S, Roberts I, Dirnagl U, Chalmers I, Ioannidis JPA, Salman RA-S, Chan A-W, Glasziou P. Biomedical research: increasing value, reducing waste. Lancet 2017;383:101–104.

[36] McDonald L, Schultze A, Simpson A, Graham S, Wasiak R, Ramagopalan S V. Lack of data sharing in observational studies. Bmj 2017;359:j4866.

[37] McDonald L, Schultze A, Simpson A, Graham S, Wasiak R, Ramagopalan S V. A review of data sharing statements in observational studies published in the BMJ: A cross-sectional study. F1000Research 2017;6:1708.

[38] McKeown A, Gewandter JS, McDermott MP, Pawlowski JR, Poli JJ, Rothstein D, Farrar JT, Gilron I, Katz NP, Lin AH, Rappaport B a., Rowbotham MC, Turk DC, Dworkin RH, Smith SM. Reporting of Sample Size Calculations in Analgesic Clinical Trials: ACTTION Systematic Review. J Pain 2015;16:199–206.e7.

[39] McKiernan EC, Bourne PE, Brown CT, Buck S, Kenall A, Lin J, McDougall D, Nosek BA, Ram K, Soderberg CK, Spies JR, Thaney K, Updegrove A, Woo KH, Yarkoni T. How open science helps researchers succeed. Elife 2016;5:1–19.

[40] Miguel E, Camerer C, Casey K, Cohen J, Esterling KM, Gerber A, Glennerster R, Green DP, Humphreys M, Imbens G. Promoting transparency in social science research. Science 2014;343:30–31.

[41] Mogil JS, Macleod MR. No publication without confirmation. Nature 2017;542:409–411.

[42] Moher D, CS D, GA W. Statistical power, sample size, and their reporting in randomized controlled trials. Jama 1994;272:122–124.

[43] Moher D, Schulz KF, Simera I, Altman DG. Guidance for developers of health research

reporting guidelines. PLoS Med 2010;7:e1000217.

[44] Morey RD, Chambers CD, Etchells PJ, Harris CR, Hoekstra R, Lakens D, Lewandowsky S, Morey CC, Newman DP, Schönbrodt FD, Vanpaemel W, Wagenmakers E-J, Zwaan RA. The Peer Reviewers' Openness Initiative: incentivizing open research practices through peer review. R Soc Open Sci 2016;3:150547.

[45] Moseley GL. Finding the love between scientists and clinicians – a response to Dr Butler on noijam. BodyinMind 2013. Available: https://bodyinmind.org/finding-the-love-between-scientists-and-clinicians-a-response-to-dr-butler-on-noijam/.

[46] Moseley GL. Re: Antibiotics for back pain: hope or hype? Bmj Response 2013:346:f3122.

[47] Munafò MR, Nosek BA, Bishop DVM, Button KS, Chambers CD, Percie du Sert N, Simonsohn U, Wagenmakers E, Ware JJ, Ioannidis JPA. A manifesto for reproducible science. Nat Hum Behav 2017;1:1–9.

[48] Nosek BA, Alter G, Banks GC, Borsboom D, Bowman SD, Breckler SJ, Buck S, Chambers CD, Chin G, Christensen G, Contestabile M, Dafoe A, Eich E, Freese J, Glennerster R, Goroff D, Green DP, Hesse B, Humphreys M, Ishiyama J, Karlan D, Kraut A, Lupia A, Mabry P, Madon T, Malhotra N, Mayo-Wilson E, McNutt M, Miguel E, Paluck EL, Simonsohn U, Soderberg C, Spellman BA, Turitto J, VandenBos G, Vazire S, Wagenmakers EJ, Wilson R, Yarkoni T. Promoting an open research culture. Science 2015;348:1422–1425.

[49] Nosek BA, Lakens D. Registered reports: A method to increase the credibility of published results. Soc Psychol (Gott) 2014;45:137–141.

[50] Open Science Collaboration. Estimating the reproducibility of psychological science. Science 2015;349.

[51] Patil P, Peng RD, Leek JT. A statistical definition for reproducibility and replicability. BioRxiV 2017;Preprint.

[52] Peng RD, Dominici F, Zeger SL. Reproducible epidemiologic research. Am J Epidemiol 2006;163:783–789.

[53] Perneger T, Combescure C. The distribution of P-values in medical research articles suggested

selective reporting associated with statistical significance. J Clin Epidemiol 2017;87:70–77.

[54] Piccolo SR, Frampton MB. Tools and techniques for computational reproducibility. Gigascience 2016;5:30.

[55] Poldrack RA, Baker CI, Durnez J, Gorgolewski KJ, Matthews PM, Munafò M, Nichols TE, Poline J-B, Vul E, Yarkoni T. Scanning the Horizon: Towards transparent and reproducible neuroimaging research. Nat Rev Neurosci 2016;18:115–126.

[56] Portney LG, Watkins MP. Foundations of clinical research: applications to practice. Prentice Hall, 2000.

[57] Rawat S, Meena S. Publish or perish: Where are we heading? J Res Med Sci 2014;19:87–89.

[58] Reid EJ, Braithwaite FA, Wallwork SB, Harvie D, Chalmers KJ, Spence C, Gallace A, Moseley GL. Spatially-defined motor deficits in people with unilateral complex regional pain syndrome. Cortex 2017 (online first).

[59] Rice ASC, Morland R, Huang W, Currie GL, Sena ES, Macleod MR. Transparency in the reporting of in vivo pre-clinical pain research: The relevance and implications of the ARRIVE (Animal Research: Reporting In Vivo Experiments) guidelines. Scand J Pain 2013;4:58–62.

[60] Robertson M. Who needs registered reports? BMC Biol 2017;15:49.

[61] Rosenbaum L. Bridging the Data-Sharing Divide — Seeing the Devil in the Details, Not the Other Camp. N Engl J Med 2017;376:2201–2203.

[62] Rowbotham MC. The case for publishing “negative” clinical trials. Pain 2009;146:225–226.

[63] Scientific data. Nature. Available: https://www.nature.com/sdata/. Accessed 8 Feb 2018.

[64] Shanahan DR, Lopes De Sousa I, Marshall DM. Simple decision-tree tool to facilitate author identification of reporting guidelines during submission: a before–after study. Res Integr Peer Rev 2017;2:1–6.

[65] Sharing Clinical Trial Data: what it means for you. Wellcome 2017. Available: https://wellcome.ac.uk/news/sharing-clinical-trial-data-what-it-means-you. Accessed 8 Feb 2018.

[66] Simera I, Moher D, Hirst A, Hoey J, Schulz KF, Altman DG. Transparent and accurate

reporting increases reliability, utility, and impact of your research: Reporting guidelines and the EQUATOR Network. BMC Med 2010;8:24.

[67] Simmons JP, Nelson LD, Simonsohn U. False-Positive Psychology: Undisclosed Flexibility in Data Collection and Analysis Allows Presenting Anything as Significant. Psychol Sci 2011;22:1359–1366.

[68] Smaldino PE, McElreath R. The Natural Selection of Bad Science. R Soc Open Sci 2016;3:160384.

[69] Smith SM, Hunsinger M, McKeown A, Parkhurst M, Allen R, Kopko S, Lu Y, Wilson HD, Burke LB, Desjardins P, McDermott MP, Rappaport BA, Turk DC, Dworkin RH. Quality of pain intensity assessment reporting: ACTTION systematic review and recommendations. J Pain 2015;16:299–305.

[70] Smith SM, Wang AT, Pereira A, Chang RD, McKeown A, Greene K, Rowbotham MC, Burke LB, Coplan P, Gilron I, Hertz SH, Katz NP, Lin AH, McDermott MP, Papadopoulos EJ, Rappaport BA, Sweeney M, Turk DC, Dworkin RH. Discrepancies between registered and published primary outcome specifications in analgesic trials: ACTTION systematic review and recommendations. Pain 2013;154:2769–2774.

[71] Taichman DB, Backus J, Baethge C, Bauchner H, Leeuw PW de, Drazen JM, Fletcher J, Frizelle FA, Groves T, Haileamlak A, James A, Laine C, Peiperl L, Pinborg A, Sahni P, Wu S. Sharing clinical trial data. Bmj 2016;255:i255.

[72] Taichman DB, Sahni P, Pinborg A, Peiperl L, Laine C, James A, Hong S-T, Haileamlak A, Gollogly L, Godlee F, Frizelle FA, Florenzano F, Drazen JM, Bauchner H, Baethge C, Backus J. Data Sharing Statements for Clinical Trials — A Requirement of the International Committee of Medical Journal Editors. N Engl J Med 2017;376:2277–2279.

[73] The BMC Medicine team. BMC Medicine becomes the first medical journal to accept Registered Reports. BMC Blog Network 2017. Available: http://blogs.biomedcentral.com/bmcblog/2017/08/24/bmc-medicine-becomes-the-first-medical-journal-to-accept-registered-reports/. Accessed 22 Nov 2017.

[74] Wicherts JM, Veldkamp CLS, Augusteijn HEM, Bakker M, van Aert RCM, van Assen MALM. Degrees of freedom in planning, running, analyzing, and reporting psychological studies: A checklist to avoid P-hacking. Front Psychol 2016;7:1–12.

[75] Wilkinson MD, Dumontier M, Aalbersberg IjJ, Appleton G, Axton M, Baak A, Blomberg N, Boiten J-W, da Silva Santos LB, Bourne PE, Bouwman J, Brookes AJ, Clark T, Crosas M, Dillo I, Dumon O, Edmunds S, Evelo CT, Finkers R, Gonzalez-Beltran A, Gray AJG, Groth P, Goble C, Grethe JS, Heringa J, Hoen PA. 't, Hooft R, Kuhn T, Kok R, Kok J, Lusher SJ, Martone ME, Mons A, Packer AL, Persson B, Rocca-Serra P, Roos M, van Schaik R, Sansone S-A, Schultes E, Sengstag T, Slater T, Strawn G, Swertz M a., Thompson M, van der Lei J, van Mulligen E, Velterop J, Waagmeester A, Wittenburg P, Wolstencroft K, Zhao J, Mons B. The FAIR Guiding Principles for scientific data management and stewardship. Sci Data 2016;3:160018.

[76] Xie Y. knitr: a comprehensive tool for reproducible research in R. Implement Reprod Res 2014;1:20.

[77] Zorzela L, Golder S, Liu Y, Pilkington K, Hartling L, Joffe A, Loke Y, Vohra S. Quality of reporting in systematic reviews of adverse events: systematic review. Bmj 2014;348:f7668.

FIGURE CAPTIONS

Figure 1. Distinguishing reproducibility and replicability

Each panel depicts the requirements for reproducibility (left) and replicability (right). Blue boxes represent study components that do not change in the process of reproducing/replicating the original study. Red boxes represent study components that change in the process of reproducing/replicating the original study. Reproducing a study involves independent researchers analysing the same data and getting the same result. Replicating a study involves independent researchers collecting new data, analysing it and getting the same result. Thus, reproducibility is necessary but not sufficient for replication. Figure adapted from Patil et al. (2017) [51].

Table 1. Transparency standards of 10 leading pain journals

Journal	Pre-registration	Registered reports	Data sharing	Data sharing statement	Sharing code	Reporting guidelines	TOP signatory
Pain	Required for all clinical trials	Not mentioned	Encouraged*	Required*	Encouraged*	Requires: CONSORT, TIDieR, SPIRIT Encourages other relevant guidelines via EQUATOR Network (eg. COBIDAS) *	No
Journal of pain	Required for all clinical trials	Not mentioned	Encouraged	Encouraged	Encouraged	Requires: ARRIVE, CONSORT, PRISMA, STARD, and STROBE	Yes
Journal of headache and pain	Required for all clinical trials Encouraged for systematic reviews	Not mentioned	Encouraged	Required	Encouraged	Encourages: CONSORT, SPIRIT, PRISMA, PRISMA-P, STROBE, CARE, COREQ, STARD, TRIPOD, CHEERS, ARRIVE, or another relevant guideline from the EQUATOR Network	No
Molecular pain	Required for all clinical trials	Not mentioned	Not mentioned	Not mentioned	Not mentioned	Requires use of relevant guidelines (EQUATOR Network)	Yes
Regional anesthesia and pain medicine	Required for all clinical trials	Not mentioned	Not mentioned	Not mentioned	Not mentioned	Encourages: CONSORT, STROBE, PRISMA, CARE, ARRIVE, AGREE, or another relevant guideline from the EQUATOR Network	No
Clinical journal of pain	Not mentioned	Not mentioned	Not mentioned	Not mentioned	Not mentioned	Not mentioned	No
European journal of pain	Required for all clinical trials	Not mentioned	Encouraged	Encouraged	Not mentioned	Requires: CONSORT, PRISMA	No
Journal of pain and symptom management	Not mentioned	Not mentioned	Encouraged	Encouraged	Encouraged	Not mentioned	Yes
Pain physician	Required for all clinical trials	Not mentioned	Not mentioned	Not mentioned	Not mentioned	Encourages: PRISMA, MOOSE, CONSORT, SPIRIT, STROBE, TREND, ARRIVE, STARD	No
Pain medicine	Not mentioned	Not mentioned	Not mentioned	Not mentioned	Not mentioned	Not mentioned	No

This table represents the current level of engagement with minimum transparency research standards as suggested by The Transparency and Openness Promotion (TOP) Committee (ref Nosek et al 2016). Journals were selected by identifying top 10 pain journals ranked by impact factor - Web of Science, InCites Journal Citation Reports (Clarivate Analytics) – 2016 Journal Citation Reports. Snapshot of the author guidelines and journal policies were taken on 09/02/2018, and data were extracted by two independent reviewers.

* Not mentioned in author guidelines but taken from Keefe et al. 2018 Pain.

REPRODUCIBILITY

Study 1	*Study 2*
Population	Population
Research Question / Hypothesis	Research Question / Hypothesis
Study design	Study design
Study personnel (e.g. outcome assessor)	Study personnel (e.g. outcome assessor)
Data	Data
Analysis plan	Analysis plan
Code	Code
Analyst	Different Analyst

Study 2 has successfully ***reproduced*** Study 1 if the estimates from both studies are consistent

REPLICABILITY

Study 1	*Study 2*
Population	Population
Research Question / Hypothesis	Research Question / Hypothesis
Study design	Study design
Study personnel (e.g. outcome assessor)	Different Study personnel
Data	New Data
Analysis plan	Analysis plan
Code	New Code
Analyst	Different Analyst

Study 2 has successfully ***replicated*** Study 1 if the estimates from both studies are consistent