University of Dundee

Translating clinical trials into improved real-world management of pain

Gilron, Ian; Blyth, Fiona M.; Smith, Blair

Published in:
Pain

DOI:
[10.1097/j.pain.0000000000001684](https://doi.org/10.1097/j.pain.0000000000001684)

Publication date:
2020

Document Version
Peer reviewed version

[Link to publication in Discovery Research Portal](#)

Citation for published version (APA):

Gilron, I., Blyth, F. M., & Smith, B. (2020). Translating clinical trials into improved real-world management of pain: Convergence of translational, population-based and primary care research. *Pain*, 161(1), 36-42.
<https://doi.org/10.1097/j.pain.0000000000001684>

General rights

Copyright and moral rights for the publications made accessible in Discovery Research Portal are retained by the authors and/or other copyright owners and it is a condition of accessing publications that users recognise and abide by the legal requirements associated with these rights.

- Users may download and print one copy of any publication from Discovery Research Portal for the purpose of private study or research.
- You may not further distribute the material or use it for any profit-making activity or commercial gain.
- You may freely distribute the URL identifying the publication in the public portal.

Take down policy

If you believe that this document breaches copyright please contact us providing details, and we will remove access to the work immediately and investigate your claim.

PAIN

Translating clinical trials into improved real-world management of pain: Convergence of translational, population-based and primary care research --Manuscript Draft--

Manuscript Number:	PAIN-D-19-00379R2
Full Title:	Translating clinical trials into improved real-world management of pain: Convergence of translational, population-based and primary care research
Article Type:	Topical Review (INVITED ONLY)
Keywords:	Clinical trials; population health; Primary care; chronic pain; implementation science
Corresponding Author:	Ian Gilron, MD, MSc, FRCPC Queen's University Kingston, Ontario CANADA
Corresponding Author Secondary Information:	
Corresponding Author's Institution:	Queen's University
Corresponding Author's Secondary Institution:	
First Author:	Ian Gilron, MD, MSc, FRCPC
First Author Secondary Information:	
Order of Authors:	Ian Gilron, MD, MSc, FRCPC
	Fiona Blyth, PhD, MBBS
	Blair H Smith, MD
Additional Information:	
Question	Response
Have you posted this manuscript on a preprint server (e.g., arXiv.org, BioXriv, PeerJ Preprints)?	No

Translating clinical trials into improved real-world management of pain: Convergence of translational, population-based and primary care research

Ian Gilron, MD, MSc, FRCPC¹, Fiona Blyth, PhD, MBBS², Blair H Smith, MD³

¹Department of Anesthesiology & Perioperative Medicine, Queen's University and Kingston Health Sciences Centre, Kingston, Ontario, Canada

²The University of Sydney, Centre for Education and Research on Ageing, Sydney, Australia

³Division of Population Health and Genomics, School of Medicine, University of Dundee, Ninewells Hospital and Medical School, Dundee, DD2 4BF, Scotland

Corresponding author:

Ian Gilron, MD, MSc, FRCPC
Director of Clinical Pain Research
Professor of Anesthesiology & Perioperative Medicine,
Biomedical & Molecular Sciences, and Centre for
Neuroscience Studies
Queen's University and
Kingston Health Sciences Centre

Number of figures: 3

Number of tables: 0

Word count: 2,717

References: 101

1. Introduction

Many strategies may guide improved pain treatment. Among these are: 1) translational research (e.g. clinical trials of novel therapies emerging from basic science); 2) population research (e.g. identify pain burden-pain care health service gaps and describe treatment harms); and, 3) primary care research (e.g. describe patient presentation/referral patterns, treatment preferences/goals, develop patient care models/pathways). As in Figure 1, convergence of these strategies can help determine who needs treatment, whether treatments are effective, and how to administer treatments.

Evidence from randomized controlled trials (RCTs) guides early implementation of new treatments and represents the translational link between preclinical research and patient care [25,30,55,65,99]. Controlled phase 1, 2 and 3 RCTs demonstrate safety and efficacy to justify marketing approval of new treatments [23,34,36,98,100]. Knowledge synthesis of multiple RCTs of a treatment, e.g. systematic reviews and meta-analyses, facilitates evidence-based clinical decisions [1,59,64]. “Evidence-based medicine” facilitates treatment selection based on consideration of all available safety and efficacy evidence, sometimes including non-controlled studies and expert opinion [29,40,43,80].

The narrow focus of phase 1-3 RCTs necessitates additional, larger, phase 4 post-marketing studies for safety and efficacy evidence in broader populations [11,75]. However, even phase 4 studies have limitations in generalizing to widespread use, and post-marketing recognition of problems with anti-inflammatory drugs [47,63] and opioids [21,56] has emphasized important gaps between RCTs and real-world practice [62]. Furthermore, statistically significant efficacy (e.g. treatment-placebo difference) in RCTs sometimes translates to a questionably meaningful effect [24,40,73]. Such gaps are related to differences in RCT, versus real-world, conditions and emphasize the need for pharmacoepidemiologic, database-driven and other large cohort population research [38,39,82].

Most patient encounters involve primary care providers [20,86,87,94] and challenges in this setting include recognition/prioritization of chronic pain among other competing clinical problems

[66,94]. Further challenges include identifying safe, cost-effective and evidence-based multimodal interventions [17,31,66] and revising practices in response to emerging evidence [41]. As in Figure 2, evaluating a new treatment evolves through stages of translational, population-based and primary care research. This article reviews challenges to implementation of pain treatments that may be overcome with closer integration of 1) population-based, 2) translational, and 3) real-world, primary care research.

2. Population-based research on chronic pain burden and impact of pain treatment

Chronic pain is a major contributor to the global health burden of non-fatal disease [9,95]. Pain treatment trials should therefore be implemented as part of a complex set of strategies to prevent and control the population impact of pain. Thus, RCTs can inform both chronic pain prevention but also chronic pain burden reduction. Complementary to RCTs, pharmacoepidemiology – the study of the use and effects of drugs in large numbers of people [90] – is characterized by various epidemiological methods, study designs, and data sources to examine patterns of medication use and associated population impact. This impact is broadly defined to include benefits and the harms of medicine use across different population levels (individuals, communities, and population as a whole).

Also, a population perspective may identify evidence-burden gaps in existing trials, and future questions where evidence is most needed. For example, chronic pain prevalence is associated with ageing and analgesic use is common in older (e.g. >65 years old) patients [49], yet this population is commonly excluded from RCTs [6]. Another critical gap in the generalizability of pain RCTs is the recognition that a substantial number of people with chronic pain have multiple pain etiologies and anatomical pain sites, as well as other coexisting multimorbidities [74] that often exclude them from classical RCTs with tight exclusion criteria. These well-recognized problems for RCTs – in many areas – reveal a limited understanding of drug-drug, and drug-disease interactions relevant for older, multimorbid populations on multiple medications and require future study.

As evidence of an important evidence-burden gap, a recent analysis compared registered RCTs within 27 disease groupings against burden of disease data across seven global regions [3]. This study found a widespread mismatch between trials and disease burden for musculoskeletal conditions in all income level strata. Furthermore, other differences – with respect to pain prevalence and treatment – in sex/gender [51], race/ethnicity [14;33] and comorbidities [74] suggest other important evidence-burden gaps in real-world pain treatment and research.

Thus, evidence suggests a mismatch between trials and population pain burden, and that closer alignment between RCTs and population-focused studies would better contribute to chronic pain prevention and control at a population level.

3. Methodology of translational RCTs and barriers to their implementation into clinical practice

A prototypical design for a phase 3 trial involves parallel randomization of participants to two or more treatment arms including: 1) the study treatment, 2) a placebo control, and 3) a different dose of the study treatment, or a different treatment comparator [25,96]. A major trial design focus is internal validity (e.g. precision and accuracy), and minimization of bias, requiring random allocation of participants to treatment group, blinding of participants and researchers to treatment allocation, and other important factors including sample size, treatment duration, and, duration/completeness of outcome follow-up [1,48].

Broadly, RCTs, which are diverse in design and purpose, collectively strive for internal validity (e.g. assay sensitivity), external validity (e.g. generalizability), risk-benefit evaluation and cost-benefit evaluation (Figure 3). However, RCTs vary depending on the purpose and research question. An important dichotomy articulated by Schwartz and Lellouch, was between an ‘explanatory’ trial – aiming to demonstrate a biological principle – versus a ‘pragmatic’ trial – aiming to guide treatment choices [83]. This dichotomy remains relevant with divergent purposes such as: 1) industry-sponsored RCTs to demonstrate safety and efficacy to support marketing a new treatment; and 2) ‘academic’ RCTs of available treatments to inform best practices. Explanatory trials – commonly product development trials scrutinized by regulatory agencies – focus on feasibility, internal validity and *assay sensitivity* (ability to distinguish an effective treatment from

a less effective or ineffective treatment) [26]. Pragmatically oriented trials emphasize clinical importance of outcomes and treatment differences as well as generalizability (external validity) [24,76,77,97]. In new treatment development, ‘phase 3’, confirmatory trials inform the decision to market the product [23,34,36,98]. Fairly recently, the PRECIS-2 tool was validated for the purpose of guiding the design of clinical trials along a continuum from “very explanatory” to “very pragmatic” [61]. In this paper we mostly focus on RCTs of pharmacological pain therapies, as this is where most of the evidence currently exists. However, the principles and challenges discussed generally also apply to trials of nonpharmacological approaches, including multimodal, interdisciplinary management [52;53], which generally require more complex study designs [8;57].

RCTs need a study population sufficiently homogeneous to facilitate recruitment efficiency and maximize assay sensitivity; yet sufficiently broad and generalizable. Barriers to RCT generalizability [76,77] include trials conducted in populations with different socio-demographic characteristics different from the target healthcare setting, or in healthcare systems with different access or health insurance criteria. Further, the use of participant selection criteria that exclude important patient subgroups or comorbidities limits applicability of findings. Major psychiatric disease [93], cognitive dysfunction [81], and substance use disorder [70] are some examples of patients that might be problematic in a trial (e.g. risk of unreliable/incomplete data), but who would benefit from relevant evidence in clinical practice. Thus, consideration is needed on how to conduct trials in complex and high pain burden patient populations [28]. Here, there may be a role for pragmatic trials, conducted in real-world practice, with populations that represent those at whom the intervention is targeted (e.g. co-existing conditions, primary care setting). Some of these issues of external validity and applicability to real-world practice may be addressed with relatively novel pragmatic trial designs [32,78] such as: 1) a cluster randomised trial design whereby study interventions are randomized at the level of the practitioner, or healthcare institution – instead of at the level of the patient [20]; 2) an enriched enrolment randomised withdrawal design, which include only those who tolerate and respond to the treatment [37; 68]; and, 3) a stepped wedge design – a cluster design whereby all participants eventually receive the intervention [46].

1 Selection of trial outcome measures is also critical [22,35,50,91,92]. In 2003, the “IMMPACT”
2 group of authors (immpact.org) with expertise in pain research, drug regulation and the pain
3 therapeutics industry recommended the following core outcome domains for pain trials: pain,
4 physical and emotional function, treatment satisfaction, participant disposition through the trial
5 (e.g. early withdrawal due to adverse effects) and treatment-emergent adverse events [22,91].
6 Since most novel pain therapies have demonstrated efficacy in preclinical models of nociception
7 and pain [34], it is logical that pain intensity be used as a primary outcome measure. However, in
8 practice, pain management does not always result in substantial reductions in pain intensity. This
9 may be due to limited treatment efficacy, dose-limiting treatment side effects, or, analgesia-
10 related increases in physical activity that subsequently increase pain. Despite this, pain
11 management may result in other benefits including improved coping, physical function, mood and
12 sleep even if pain intensity reduction is not always apparent. In this regard, it is interesting to note
13 recent evidence suggesting that the use of a composite outcome measure of both pain intensity
14 and physical function may facilitate improved assay sensitivity of chronic pain RCTs [52] and so,
15 perhaps trials need not rely exclusively on pain intensity as a primary outcome measure. Thus,
16 evidence from trials, reportedly ‘positive’ for the primary outcome of pain intensity, should be
17 carefully evaluated with respect to other secondary outcomes (e.g. function, mood, sleep) [71]
18 and important adverse effects to put the treatment in appropriate clinical context for real-world
19 practice [73]. In terms of treatment safety, evidence emphasizes the need to improve assessment
20 and reporting of treatment-emergent adverse effects in pain trials [88,89], and further, to consider
21 emerging population-based evidence of potential treatment-related harms of currently used pain
22 treatments [21,47,56,63].
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44

45 Rigorous systematic review and meta-analysis is necessary to synthesize evidence from multiple
46 RCTs [64]. A commonly used metric in pain trial meta-analyses is the “number-needed-to-treat”
47 (NNT). NNT is the inverse of the absolute risk reduction in a group of trials, and represents the
48 average number of individuals who need to be treated in order for one to obtain pain relief (e.g.
49 30% pain reduction). However, this hides a wide range of individual variation in responses: a high
50 NNT could represent an intervention with which every recipient obtains just a little relief, or one
51 that provides no relief for most but excellent relief for few. For example, pregabalin demonstrated
52
53
54
55
56
57
58
59
60
61
62
63
64
65

an NNT of 7.2 for neuropathic pain in a recent systematic review [31], but Moore et al [67] demonstrated its use in a trial involving 200 people with fibromyalgia in which the range of relief obtained was 0 to almost 100%. Their message was, “Expect analgesic failure; pursue analgesic success” – in other words, even when a drug’s NNT, based on high quality trials, is high, there is still a chance of success with its use in individuals, so long as careful follow-up and early review empowers its cessation in the event of insufficient pain relief [67].

Further translation of trial-based evidence into real-world practice requires input from multiple disciplines as proposed by the GRADE (Grading of Recommendations Assessment, Development, and Evaluation) process. GRADE integrates quality of evidence, balance between beneficial and adverse effects, consideration of patient/public values and preferences and related use of resources [4,5,42]. For example, the IASP Neuropathic Pain Special Interest Group conducted a review of neuropathic pain pharmacotherapy involving systematic review and meta-analysis of treatment-specific trials, GRADE assessment and, ultimately, treatment recommendations [31].

4. Implementation of research evidence into real-world, primary care, chronic pain management and research strategies

Due to the need for a comprehensive assessment and differential diagnosis of a presenting pain complaint, primary care physicians are commonly one of the first healthcare providers to evaluate an emerging chronic pain condition and to initiate early treatment approaches. Primary care has been defined as ‘first-contact, accessible, continued, comprehensive and coordinated care’ [101]. It is characterized by numerous, brief appointments between patients and multi-disciplinary healthcare professionals led by general practitioners. A primary care consultation (typically 10 minutes) is multi-factorial and restricted by the short time available [72]. Thus, ready access to evidence about treatment interventions is essential to effective primary care – particularly relevant to pain management, which accounts for 22% to 50% of primary care consultations (while only 0.3% to 2% with chronic pain are referred to specialist pain clinics) [86]. Recognition of time constraints and patient complexity has encouraged a medical model with prescribed medicines, which are straightforward to implement, and meet the apparent needs or expectations of both

1 patient and professional [15]. However, it has been recently noted that an emphasis on prescribed
2 medicines may preclude alternative or complementary non-pharmaceutical approaches such as
3 self-management, physical, and psychological therapies [85] that are more time intensive. This has
4 led to the introduction and study of alternative care models [60] including: 1) ‘stepped care’ –
5 provision of condition-specific, guideline-based treatments with a progression to more complex or
6 invasive intervention as required [27]; 2) ‘stratified care’ – provision of treatment intensiveness
7 and comprehensiveness according to patient factors (e.g. low, medium and high risk) [7]; and 3)
8 ‘matched’ care – individualizing specific treatments to patient factors that predict need or
9 favourable response [2]. Furthermore, the optimal implementation of such novel health care
10 models require adoption, scalability and sustainability at a health system level [10].
11
12
13
14
15
16
17
18
19
20
21

22 Although efforts to improve implementation of, and access to, nonpharmacological pain
23 treatments are expanding, the current reality is that analgesic drug prescribing remains one of the
24 most common examples of pain management in primary care settings. Safe and effective analgesic
25 prescribing requires careful discussion and frequent review, often with slow titration to
26 appropriate effective and tolerated doses. This is difficult to achieve with traditional physician-led
27 primary care. Alternative models of care are therefore required, including non-medical
28 prescribing, nurse- or pharmacist-led pain clinics, and shared decision support systems.
29
30
31
32
33
34
35

36 “Independent Prescribing” is available in the UK, with training and qualifications, to non-physician
37 health professionals [19]. With required qualifications, they can prescribe medicines within their
38 level of expertise. One study found that pain was the second most prevalent area for which nurses
39 prescribed [18]. Studies of nurse-led, or pharmacist-led, pain clinics reported efficient and
40 effective results and favourable treatment outcomes [12,44,45,58,79]. Building on this, Scotland
41 has developed a national prescribing strategy that combines evidence with results of locally
42 implemented prescribing approaches [69]. Decisions based on risk-benefit considerations can be
43 facilitated by Clinical Decision Support Systems that follow algorithms integrated into healthcare
44 computer systems and patient-facing apps. These under development for chronic pain [84].
45
46
47
48
49
50
51
52
53

54 As alluded to above, lessons learned from the opioid crisis have emphasized the potential value of
55 expanding implementation and access to nondrug treatments for pain as well as pain
56 management team leadership to also involve a broader range of health professionals. In fact,
57
58
59
60
61
62
63
64
65

interdisciplinary pain treatment teams led by psychologists and other, non-physician, health professionals have been successful for many years in some places, and emerging evidence suggests that chronic pain patients treated at facilities that provide nondrug pain treatments are less likely to initiate long term opioid therapy [13]. Thus, with a growing impetus to pursue nondrug pain treatments, such as various physical and psychological interventions, the synthesis and implementation of RCT evidence of these interventions is similarly needed [16; 54].

5. Conclusion

This review highlights barriers to the implementation of RCT evidence into patient care. At a population level, continued efforts to identify various populations with high pain burden should be coupled with new RCTs involving comparable, high pain burden, populations. Given the short duration of RCTs, more pharmacoepidemiologic studies are needed to describe harms with long-term, real-world, use of pain treatments, often used differently than they were in RCTs.

Challenges of treating pain in patients with comorbid conditions (e.g. depression, substance abuse, dementia) – that are commonly excluded from traditional RCTs – suggest a need for trials that feasibly include such complex patients. Other future improvements require RCTs to focus on populations with greater pain burden through careful attention to patient factors such as sex/gender, age, race/ethnicity, socioeconomic status, geographical location and access to healthcare.

Implementing trial evidence into primary care requires expansion of resources, including a broader range of health professionals, to effectively replicate treatment conditions followed in RCTs. Further implementation success requires synthesis and translation of evidence into treatment guidelines, patient care pathways and community-oriented treatment strategies in the context of multimodal therapy.

Continued collaboration between population science, RCTs and primary care research will promote more effective implementation of emerging pain therapies to ultimately improve pain management patient outcomes.

Conflicts of interest statement

FB has no conflicts to declare. IG has received support from Biogen, Adynxx, TARIS Biomedical, AstraZeneca, Pfizer, and Johnson and Johnson and has received grants from the Canadian Institutes of Health Research, Physicians' Services Incorporated Foundation, and Queen's University. BHS has no conflicts to declare.

Acknowledgements

This topical review is based on a Topical Workshop presented by Drs. Gilron, Blyth and Smith at the IASP 17th World Congress on Pain in Boston, USA, September 2018. This work was supported, in part, by the Canadian Institutes of Health Research Strategy on Patient-Oriented Research Chronic Pain Network.

References

- [1] Andrew Moore R, Eccleston C, Derry S, Wiffen P, Bell RF, Straube S, McQuay H; ACTINPAIN Writing Group of the IASP Special Interest Group on Systematic Reviews in Pain Relief; Cochrane Pain, Palliative and Supportive Care Systematic Review Group Editors. "Evidence" in chronic pain--establishing best practice in the reporting of systematic reviews. *Pain*. 2010 Sep;150(3):386-9.
- [2] Åsenlöf P, Denison E, Lindberg P. Individually tailored treatment targeting activity, motor behavior, and cognition reduces pain-related disability: a randomized controlled trial in patients with musculoskeletal pain. *J Pain* 2005;6:588-603.
- [3] Atal I, Trinquart L, Ravaud P, Porcher R. A mapping of 115,000 randomized trials revealed a mismatch between research effort and health needs in none-high-income regions. *J Clin Epidemiol* 2018; 98:123-132.
- [4] Atkins D, Best D, Briss PA, Eccles M, Falck-Ytter Y, Flottorp S, Guyatt GH, Harbour RT, Haugh MC, Henry D, Hill S, Jaeschke R, Leng G, Liberati A, Magrini N, Mason J, Middleton P, Mrukowicz J, O'Connell D, Oxman AD, Phillips B, Schünemann HJ, Edejer T, Varonen H, Vist GE, Williams JW Jr, Zaza S; GRADE Working Group. Grading quality of evidence and strength of recommendations. *BMJ*. 2004 Jun 19;328(7454):1490.
- [5] Balshem H, Helfand M, Schünemann HJ, Oxman AD, Kunz R, Brozek J, Vist GE, Falck-Ytter Y, Meerpohl J, Norris S, Guyatt GH. GRADE guidelines: 3. Rating the quality of evidence. *J Clin Epidemiol*. 2011 Apr;64(4):401-6.
- [6] Beers E, Moerkerken DC, Leufkens HGM, Egberts TCG, Jansen PAF. Participation of Older People in Preauthorization Trials of Recently Approved Medicines. *J Am Geriatr Soc* 62:1883-1890, 2014.
- [7] Beneciuk JM, George SZ. Pragmatic implementation of a stratified primary care model for low back pain management in outpatient physical therapy settings: two-phase, sequential preliminary study. *Phys Ther* 2015;95:1120-34.
- [8] Bhimani RH, Cross LJ, Taylor BC, Meis LA, Fu SS, Allen KD, Krein SL, Do T, Kerns RD, Burgess DJ. Taking ACTION to reduce pain: ACTION study rationale, design and protocol of a randomized trial of a proactive telephone-based coaching intervention for chronic musculoskeletal pain among African Americans. *BMC Musculoskelet Disord*. 2017 Jan 13;18(1):15.
- [9] Blyth FM, Van Der Windt DA, Croft PR. Chronic Disabling Pain: A Significant Public Health Problem. *American Journal of Preventive Medicine*. 2015; 49(1):98-101.
- [10] Braithwaite J. Changing how we think about healthcare improvement. *BMJ*. 2018 May 17;361:k2014.
- [11] Brewer T, Colditz GA. Postmarketing surveillance and adverse drug reactions: current perspectives and future needs. *JAMA*. 1999 Mar 3;281(9):824-9.
- [12] Bruhn H, Bond CM, Elliott AM, Hannaford PC, Lee AJ, McNamee P, Smith BH, Watson MC, Holland R, Wright D. Pharmacist-led management of chronic pain in primary care: results from a randomised controlled exploratory trial. *BMJ Open*. 2013;3(4). pii: e002361.
- [13] Carey EP, Nolan C, Kerns RD, Ho PM, Frank JW. Association Between Facility-Level Utilization of Non-pharmacologic Chronic Pain Treatment and Subsequent Initiation of Long-Term Opioid Therapy. *J Gen Intern Med*. 2018 May;33(Suppl 1):38-45.

- [14] Carey TS, Freburger JK, Holmes GM, Jackman A, Knauer S, Wallace A, Darter J. Race, care seeking, and utilization for chronic back and neck pain: population perspectives. *J Pain*. 2010 Apr;11(4):343-50.
- [15] Chew-Graham C, May C. Chronic low back pain in general practice: the challenge of the consultation. *Fam Pract*. 1999 Feb;16(1):46-9.
- [16] Chou R, Deyo R, Friedly J, Skelly A, Hashimoto R, Weimer M, Fu R, Dana T, Kraegel P, Griffin J, Grusing S, Brodt ED. Nonpharmacologic Therapies for Low Back Pain: A Systematic Review for an American College of Physicians Clinical Practice Guideline. *Ann Intern Med*. 2017 Apr 4;166(7):493-505.
- [17] Chou R, Huffman LH; American Pain Society; American College of Physicians. Medications for acute and chronic low back pain: a review of the evidence for an American Pain Society/American College of Physicians clinical practice guideline. *Ann Intern Med*. 2007 Oct 2;147(7):505-14.
- [18] Courtenay M, Carey N, Stenner K. An overview of non medical prescribing across one strategic health authority: a questionnaire survey. *BMC Health Serv Res*. 2012;12:138.
- [19] Department of Health. Prescribing by Non-Medical Healthcare Professionals. Available at: <https://www.health-ni.gov.uk/articles/pharmaceutical-non-medical-prescribing>; 2018, Accessed April 6, 2019.
- [20] Dobscha SK, Corson K, Perrin NA, Hanson GC, Leibowitz RQ, Doak MN, Dickinson KC, Sullivan MD, Gerrity MS. Collaborative care for chronic pain in primary care: a cluster randomized trial. *JAMA*. 2009 Mar 25;301(12):1242-52.
- [21] Dunn KM, Saunders KW, Rutter CM, Banta-Green CJ, Merrill JO, Sullivan MD, Weisner CM, Silverberg MJ, Campbell CI, Psaty BM, Von Korff M. Opioid prescriptions for chronic pain and overdose: a cohort study. *Ann Intern Med*. 2010 Jan 19;152(2):85-92.
- [22] Dworkin RH, Turk DC, Farrar JT, Haythornthwaite JA, Jensen MP, Katz NP, Kerns RD, Stucki G, Allen RR, Bellamy N, Carr DB, Chandler J, Cowan P, Dionne R, Galer BS, Hertz S, Jadad AR, Kramer LD, Manning DC, Martin S, McCormick CG, McDermott MP, McGrath P, Quessy S, Rappaport BA, Robbins W, Robinson JP, Rothman M, Royal MA, Simon L, Stauffer JW, Stein W, Tollett J, Wernicke J, Witter J; IMMPACT. Core outcome measures for chronic pain clinical trials: IMMPACT recommendations. *Pain*. 2005 Jan;113(1-2):9-19.
- [23] Dworkin RH, Turk DC, Katz NP, Rowbotham MC, Peirce-Sandner S, Cerny I, Clingman CS, Eloff BC, Farrar JT, Kamp C, McDermott MP, Rappaport BA, Sanhai WR. Evidence-based clinical trial design for chronic pain pharmacotherapy: a blueprint for ACTION. *Pain*. 2011 Mar;152(3 Suppl):S107-15.
- [24] Dworkin RH, Turk DC, McDermott MP, Peirce-Sandner S, Burke LB, Cowan P, Farrar JT, Hertz S, Raja SN, Rappaport BA, Rauschkolb C, Sampaio C. Interpreting the clinical importance of group differences in chronic pain clinical trials: IMMPACT recommendations. *Pain*. 2009 Dec;146(3):238-44.
- [25] Dworkin RH, Turk DC, Peirce-Sandner S, Baron R, Bellamy N, Burke LB, Chappell A, Chartier K, Cleeland CS, Costello A, Cowan P, Dimitrova R, Ellenberg S, Farrar JT, French JA, Gilron I, Hertz S, Jadad AR, Jay GW, Kalliomäki J, Katz NP, Kerns RD, Manning DC, McDermott MP, McGrath PJ, Narayana A, Porter L, Quessy S, Rappaport BA, Rauschkolb C, Reeve BB, Rhodes T, Sampaio C, Simpson DM, Stauffer JW, Stucki G, Tobias J, White RE, Witter J. Research design considerations for confirmatory chronic pain clinical trials: IMMPACT recommendations. *Pain*. 2010 May;149(2):177-93.

- [26] Dworkin RH, Turk DC, Peirce-Sandner S, Burke LB, Farrar JT, Gilron I, Jensen MP, Katz NP, Raja SN, Rappaport BA, Rowbotham MC, Backonja MM, Baron R, Bellamy N, Bhagwagar Z, Costello A, Cowan P, Fang WC, Hertz S, Jay GW, Junor R, Kerns RD, Kerwin R, Kopecky EA, Lissin D, Malamut R, Markman JD, McDermott MP, Munera C, Porter L, Rauschkolb C, Rice AS, Sampaio C, Skljarevski V, Sommerville K, Stacey BR, Steigerwald I, Tobias J, Trentacosti AM, Wasan AD, Wells GA, Williams J, Witter J, Ziegler D. Considerations for improving assay sensitivity in chronic pain clinical trials: IMMPACT recommendations. *Pain* 2012;153:1148-58.
- [27] Edmond SN, Moore BA, Dorflinger LM, Goulet JL, Becker WC, Heapy AA, Sellinger JJ, Lee AW, Levin FL, Ruser CB, Kerns RD. Project STEP: Implementing the Veterans Health Administration's Stepped Care Model of Pain Management. *Pain Med.* 2018 Sep 1;19(suppl_1):S30-S37.
- [28] Ersek M, Herr K, Hilgeman MM, Neradilek MB, Polissar N, Cook KF, Nash P, Snow AL, McDarby M, Nelson FX. Developing a Pain Intensity Measure for Persons with Dementia: Initial Construction and Testing. *Pain Med.* 2018 Oct 3. doi:10.1093/pm/pny180. [Epub ahead of print].
- [29] Evidence-Based Medicine Working Group. Evidence-based medicine. A new approach to teaching the practice of medicine. *JAMA.* 1992 Nov 4;268(17):2420-5.
- [30] Farrar JT. Advances in clinical research methodology for pain clinical trials. *Nat Med.* 2010 Nov;16(11):1284-93.
- [31] Finnerup NB, Attal N, Haroutounian S, McNicol E, Baron R, Dworkin RH, Gilron I, Haanpää M, Hansson P, Jensen TS, Kamerman PR, Lund K, Moore A, Raja SN, Rice AS, Rowbotham M, Sena E, Siddall P, Smith BH, Wallace M. Pharmacotherapy for neuropathic pain in adults: a systematic review and meta-analysis. *Lancet Neurol.* 2015 Feb;14(2):162-73.
- [32] Ford I, Norrie J. Pragmatic Trials. *N Engl J Med.* 2016 Aug 4;375(5):454-63.
- [33] Gaither JR, Gordon K, Crystal S, Edelman EJ, Kerns RD, Justice AC, Fiellin DA, Becker WC. Racial disparities in discontinuation of long-term opioid therapy following illicit drug use among black and white patients. *Drug Alcohol Depend.* 2018 Nov 1;192:371-376.
- [34] Gilron I, Dickenson AH. Emerging drugs for neuropathic pain. *Expert Opin Emerg Drugs.* 2014 Sep;19(3):329-41.
- [35] Gilron I, Jensen MP. Clinical trial methodology of pain treatment studies: selection and measurement of self-report primary outcomes for efficacy. *Reg Anesth Pain Med.* 2011 Jul-Aug;36(4):374-81.
- [36] Gilron, I. Drug Discovery for Neuropathic Pain. In D.M. Simpson, J.C. McArthur, & R.H. Dworkin (eds.) *Neuropathic Pain: Mechanisms, Diagnosis, and Treatment*, 38-57. Oxford University Press, New York, 2012.
- [37] Gilron I, Wajsbrot D, Therrien F, Lemay J. Pregabalin for peripheral neuropathic pain: a multicenter, enriched enrollment randomized withdrawal placebo-controlled trial. *Clin J Pain.* 2011 Mar-Apr;27(3):185-93.
- [38] Gnjjidic D, Hilmer SN, Blyth FM, Naganathan V, Waite L, Seibel MJ, McLachlan AJ, Cumming RG, Handelsman DJ, Le Couteur DG. Polypharmacy cutoff and outcomes: five or more medicines were used to identify community-dwelling older men at risk of different adverse outcomes. *J Clin Epidemiol.* 2012 Sep;65(9):989-95.
- [39] Gomes T, Mamdani MM, Dhalla IA, Paterson JM, Juurlink DN. Opioid dose and drug-related mortality in patients with nonmalignant pain. *Arch Intern Med.* 2011 Apr 11;171(7):686-91.

- [40] Greenhalgh T, Howick J, Maskrey N; Evidence Based Medicine Renaissance Group. Evidence based medicine: a movement in crisis? *BMJ*. 2014 Jun 13;348:g3725.
- [41] Grol R, Grimshaw J. From best evidence to best practice: effective implementation of change in patients' care. *Lancet*. 2003 Oct 11;362(9391):1225-30.
- [42] Guyatt GH, Oxman AD, Vist GE, Kunz R, Falck-Ytter Y, Alonso-Coello P, Schünemann HJ; GRADE Working Group. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. *BMJ*. 2008 Apr 26;336(7650):924-6.
- [43] Guyatt GH, Sackett DL, Cook DJ. Users' guides to the medical literature. II. How to use an article about therapy or prevention. B. What were the results and will they help me in caring for my patients? Evidence-Based Medicine Working Group. *JAMA*. 1994 Jan 5;271(1):59-63.
- [44] Hadi MA, Alldred DP, Briggs M, Closs SJ. A combined nurse-pharmacist managed pain clinic: joint venture of public and private sectors. *Int J Clin Pharm*. 2012;34:1-3.
- [45] Hadi MA, Alldred DP, Briggs M, Marczewski K, Closs SJ. Effectiveness of a community based nurse-pharmacist managed pain clinic: A mixed-methods study. *Int J Nurs Stud*. 2016 Jan;53:219-27.
- [46] Hemming K, Haines TP, Chilton PJ, Girling AJ, Lilford RJ. The stepped wedge cluster randomised trial: rationale, design, analysis, and reporting. *BMJ*. 2015 Feb 6;350:h391.
- [47] Hernández-Díaz S, Rodríguez LA. Association between nonsteroidal anti-inflammatory drugs and upper gastrointestinal tract bleeding/perforation: an overview of epidemiologic studies published in the 1990s. *Arch Intern Med*. 2000 Jul 24;160(14):2093-9.
- [48] Higgins JP, Altman DG, Gøtzsche PC, Jüni P, Moher D, Oxman AD, Savovic J, Schulz KF, Weeks L, Sterne JA; Cochrane Bias Methods Group; Cochrane Statistical Methods Group. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. *BMJ*. 2011 Oct 18;343:d5928.
- [49] Jackson T, Thomas S, Stabile V, Shotwell M, Han X, McQueen KA. A systematic review and meta-analysis of the global burden of chronic pain without clear etiology in low- and middle-income countries: trends in heterogeneous data and a proposal for new assessment methods. *Anesth Analg*. 2016;123:739–748.
- [50] Jensen MP, Wang W, Potts SL, Gould EM. The meaning of global outcome measures in pain clinical trials: more than just change in pain intensity. *Clin J Pain*. 2013 Apr;29(4):289-95.
- [51] Jiménez-Trujillo I, López-de-Andrés A, Del Barrio JL, Hernández-Barrera V, Valero-de-Bernabé M, Jiménez-García R. Gender Differences in the Prevalence and Characteristics of Pain in Spain: Report from a Population-Based Study. *Pain Med*. 2019 Feb 21. pii: pnz004.
- [52] Kaiser U, Treede RD, Sabatowski R. Multimodal pain therapy in chronic noncancer pain- gold standard or need for further clarification? *Pain*. 2017 Oct;158(10):1853-1859.
- [53] Kerns RD, Krebs EE, Atkins D. Making Integrated Multimodal Pain Care a Reality: A Path Forward. *J Gen Intern Med*. 2018 May;33(Suppl 1):1-3.
- [54] Kligler B, Bair MJ, Banerjea R, DeBar L, Ezeji-Okoye S, Lisi A, Murphy JL, Sandbrink F, Cherkin DC. Clinical Policy Recommendations from the VHA State-of-the-Art Conference on Non-Pharmacological Approaches to Chronic Musculoskeletal Pain. *J Gen Intern Med*. 2018 May;33(Suppl 1):16-23.
- [55] Kola I, Landis J. Can the pharmaceutical industry reduce attrition rates? *Nat Rev Drug Discov*. 2004 Aug;3(8):711-5.

- [56] Kolodny A, Courtwright DT, Hwang CS, Kreiner P, Eadie JL, Clark TW, Alexander GC. The prescription opioid and heroin crisis: a public health approach to an epidemic of addiction. *Annu Rev Public Health*. 2015 Mar 18;36:559-74.
- [57] Lamb SE, Lall R, Hansen Z, Withers EJ, Griffiths FE, Szczepura A, Barlow J, Underwood MR; Back Skills Training Trial (BeST) Team. Design considerations in a clinical trial of a cognitive behavioural intervention for the management of low back pain in primary care: Back Skills Training Trial. *BMC Musculoskelet Disord*. 2007 Feb 22;8:14.
- [58] Laurant M, van der Biezen M, Wijers N, Watananirun K, Kontopantelis E, van Vught AJ. Nurses as substitutes for doctors in primary care. *Cochrane Database Syst Rev*. 2018 Jul 16;7:CD001271.
- [59] Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gøtzsche PC, Ioannidis JP, Clarke M, Devereaux PJ, Kleijnen J, Moher D. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate healthcare interventions: explanation and elaboration. *BMJ*. 2009 Jul 21;339:b2700.
- [60] Linton SJ, Nicholas M, Shaw W. Why wait to address high-risk cases of acute low back pain? A comparison of stepped, stratified, and matched care. *Pain*. 2018 Dec;159(12):2437-2441.
- [61] Loudon K, Treweek S, Sullivan F, Donnan P, Thorpe KE, Zwarenstein M. The PRECIS-2 tool: designing trials that are fit for purpose. *BMJ*. 2015 May 8;350:h2147.
- [62] Martin K, Bégaud B, Latry P, Miremont-Salamé G, Fourrier A, Moore N. Differences between clinical trials and postmarketing use. *Br J Clin Pharmacol*. 2004 Jan;57(1):86-92.
- [63] McGettigan P, Henry D. Cardiovascular risk and inhibition of cyclooxygenase: a systematic review of the observational studies of selective and nonselective inhibitors of cyclooxygenase 2. *JAMA*. 2006 Oct 4;296(13):1633-44.
- [64] McQuay HJ, Kalso E, Moore RA editor(s). *Systematic Reviews in Pain Research: Methodology Refined*. Seattle: IASP Press, 2008.
- [65] McQuay HJ, Moore A. Methods of therapeutic trials. In: McMahon SB, Koltzenburg M, eds. *Wall and Melzack's Textbook of Pain*. 5th ed. Churchill Livingstone: Elsevier; 2006:415-425.
- [66] Mills S, Torrance N, Smith BH. Identification and Management of Chronic Pain in Primary Care: a Review. *Curr Psychiatry Rep*. 2016 Feb;18(2):22.
- [67] Moore A, Derry S, Eccleston C, Kalso E. Expect analgesic failure; pursue analgesic success. *BMJ*. 2013 May 3;346:f2690.
- [68] Moore RA, Wiffen PJ, Eccleston C, Derry S, Baron R, Bell RF, Furlan AD, Gilron I, Haroutounian S, Katz NP, Lipman AG, Morley S, Peloso PM, Quessy SN, Seers K, Strassels SA, Straube S. Systematic review of enriched enrolment, randomised withdrawal trial designs in chronic pain: a new framework for design and reporting. *Pain*. 2015 Aug;156(8):1382-95.
- [69] NHS Scotland. Effective therapeutics and prescribing – Chronic Pain Prescribing Strategy. <https://www.therapeutics.scot.nhs.uk/pain/>; 2018, Accessed April 6, 2019.
- [70] Passik SD, Kirsh KL, Donaghy KB, Portenoy RK. Pain and aberrant drug-related behaviors in medically ill patients with and without histories of substance abuse. *Clin J Pain*. 2006 Feb;22(2):173-81.
- [71] Patel KV, Allen R, Burke L, Farrar JT, Gewandter JS, Gilron I, Katz NP, Markman JD, Marshall SF, Resnick M, Rice ASC, Rowbotham MC, Smith SM, Vanhove GF, Wasan AD, Zhang S, Dworkin RH, Turk DC. Evaluation of composite responder outcomes of pain intensity and

- physical function in neuropathic pain clinical trials: an ACTION individual patient data analysis. *Pain*. 2018 Nov;159(11):2245-2254.
- [72] Irving G, Neves AL, Dambha-Miller H, Oishi A, Tagashira H, Verho A, Holden J. International variations in primary care physician consultation time: a systematic review of 67 countries. *BMJ Open*. 2017 Nov 8;7(10):e017902.
- [73] Pocock SJ, Stone GW. The Primary Outcome Is Positive - Is That Good Enough? *N Engl J Med*. 2016;375:971-9.
- [74] Ramanathan S, Hibbert P, Wiles L, Maher CG, Runciman W. What is the association between the presence of comorbidities and the appropriateness of care for low back pain? A population-based medical record review study. *BMC Musculoskelet Disord*. 2018 Nov 6;19(1):391.
- [75] Rossi AC, Knapp DE, Anello C, O'Neill RT, Graham CF, Mendelis PS, Stanley GR. Discovery of adverse drug reactions. A comparison of selected phase IV studies with spontaneous reporting methods. *JAMA*. 1983 Apr 22-29;249(16):2226-28.
- [76] Rothwell PM. External validity of randomised controlled trials: "to whom do the results of this trial apply?". *Lancet* 2005;365:82-93.
- [77] Rothwell PM. Factors that can affect the external validity of randomised controlled trials. *PLoS Clin Trials*. 2006 May;1(1):e9.
- [78] Rowbotham MC, Gilron I, Glazer C, Rice AS, Smith BH, Stewart WF, Wasan AD. Can pragmatic trials help us better understand chronic pain and improve treatment? *Pain*. 2013 May;154(5):643-6.
- [79] Ryan S, Packham JC, T Dawes P, Jordan KP. The impact of a nurse-led chronic musculoskeletal pain clinic on healthcare utilization. *Musculoskeletal Care*. 2012;10(4):196-201.
- [80] Sackett DL, Rosenberg WM, Gray JA, Haynes RB, Richardson WS. Evidence based medicine: what it is and what it isn't. *BMJ*. 1996 Jan 13;312(7023):71-2.
- [81] Scherder E, Herr K, Pickering G, Gibson S, Benedetti F, Lautenbacher S. Pain in dementia. *Pain*. 2009 Oct;145(3):276-8.
- [82] Schneeweiss S, Avorn J. A review of uses of health care utilization databases for epidemiologic research on therapeutics. *J Clin Epidemiol*. 2005 Apr;58(4):323-37.
- [83] Schwartz D, Lellouch J. Explanatory and pragmatic attitudes in therapeutic trials. *J Chron Dis* 1967;20:637-648.
- [84] Scottish Government. Practising Realistic Medicine: Chief Medical Officer for Scotland annual report. <https://www.gov.scot/publications/practising-realistic-medicine/pages/8/>; 2018, Accessed April 6, 2019.
- [85] Scottish Intercollegiate Guidelines Network. Available at: <https://www.sign.ac.uk/sign-136-management-of-chronic-pain.html>; 2013, Accessed April 6, 2019.
- [86] Smith BH, Fors EA, Korwisi B, Barke A, Cameron P, Colvin L, Richardson C, Rief W, Treede RD; IASP Taskforce for the Classification of Chronic Pain. The IASP classification of chronic pain for ICD-11: applicability in primary care. *Pain*. 2019 Jan;160(1):83-87.
- [87] Smith BH, Torrance N. Management of chronic pain in primary care. *Curr Opin Support Palliat Care*. 2011 Jun;5(2):137-42.
- [88] Smith SM, Chang RD, Pereira A, Shah N, Gilron I, Katz NP, Lin AH, McDermott MP, Rappaport BA, Rowbotham MC, Sampaio C, Turk DC, Dworkin RH. Adherence to CONSORT

- harms-reporting recommendations in publications of recent analgesic clinical trials: an ACTION systematic review. *Pain*. 2012 Dec;153(12):2415-21.
- [89] Smith SM, Wang AT, Katz NP, McDermott MP, Burke LB, Coplan P, Gilron I, Hertz SH, Lin AH, Rappaport BA, Rowbotham MC, Sampaio C, Sweeney M, Turk DC, Dworkin RH. Adverse event assessment, analysis, and reporting in recent published analgesic clinical trials: ACTION systematic review and recommendations. *Pain*. 2013 Jul;154(7):997-1008.
- [90] Strom, Brian L.; Kimmel, Stephen E; Hennessy, Sean. *Pharmacoepidemiology*. Hoboken, NJ: Wiley-Blackwell; 2011
- [91] Turk DC, Dworkin RH, Allen RR, Bellamy N, Brandenburg N, Carr DB, Cleeland C, Dionne R, Farrar JT, Galer BS, Hewitt DJ, Jadad AR, Katz NP, Kramer LD, Manning DC, McCormick CG, McDermott MP, McGrath P, Quessy S, Rappaport BA, Robinson JP, Royal MA, Simon L, Stauffer JW, Stein W, Tollett J, Witter J. Core outcome domains for chronic pain clinical trials: IMMPACT recommendations. *Pain*. 2003 Dec;106(3):337-45.
- [92] Turk DC, Dworkin RH, Burke LB, Gershon R, Rothman M, Scott J, Allen RR, Atkinson JH, Chandler J, Cleeland C, Cowan P, Dimitrova R, Dionne R, Farrar JT, Haythornthwaite JA, Hertz S, Jadad AR, Jensen MP, Kellstein D, Kerns RD, Manning DC, Martin S, Max MB, McDermott MP, McGrath P, Moulin DE, Nurmikko T, Quessy S, Raja S, Rappaport BA, Rauschkolb C, Robinson JP, Royal MA, Simon L, Stauffer JW, Stucki G, Tollett J, von Stein T, Wallace MS, Wernicke J, White RE, Williams AC, Witter J, Wyrwich KW; Initiative on Methods, Measurement and Pain Assessment in Clinical Trials. Developing patient-reported outcome measures for pain clinical trials: IMMPACT recommendations. *Pain*. 2006 Dec 5;125(3):208-15.
- [93] Turner JA, Ersek M, Kemp C. Self-efficacy for managing pain is associated with disability, depression, and pain coping among retirement community residents with chronic pain. *J Pain*. 2005 Jul;6(7):471-9.
- [94] Upshur CC, Luckmann RS, Savageau JA. Primary care provider concerns about management of chronic pain in community clinic populations. *J Gen Intern Med*. 2006 Jun;21(6):652-5.
- [95] Vos T, Abajobir AA, Abate KH, et al. Global, regional, and national incidence, prevalence, and years lived with disability for 328 diseases and injuries for 195 countries, 1990–2016: a systematic analysis for the Global Burden of Disease Study 2016. *The Lancet*. 2017;390(10100):1211-1259.
- [96] Watson CP, Gilron I, Sawynok J. A qualitative systematic review of head-to-head randomized controlled trials of oral analgesics in neuropathic pain. *Pain Res Manag*. 2010 May-Jun;15(3):147-57.
- [97] Watson CPN. External validity of pharmaceutical trials in neuropathic pain. In: Rothwell PM, ed. *Treating Individuals: From Randomised Trials to Personalised Medicine*. Philadelphia: Elsevier, 2007:121-30.
- [98] Woodcock J, Witter J, Dionne RA. Stimulating the development of mechanism-based, individualized pain therapies. *Nat Rev Drug Discov*. 2007 Sep;6(9):703-10.
- [99] Woodcock J, Woosley R. The FDA critical path initiative and its influence on new drug development. *Annu Rev Med*. 2008;59:1-12.
- [100] Woolf CJ, Max MB. Mechanism-based pain diagnosis: issues for analgesic drug development. *Anesthesiology*. 2001 Jul;95(1):241-9.
- [101] World Health Organization. Primary health care. Available at: http://www.who.int/topics/primary_health_care/en 2018; Accessed Feb 7 2019.

Figure 1: Convergent input of translational, population-based, and primary care research into the development of chronic pain treatments

Figure 2: Evolution of the implementation of pain treatments in primary care

Figure 3: Concurrent goals of clinical trials in the evaluation of chronic pain treatments

[Click here to access/download](#)

**Copyright Transfer Agreement--REQUIRED from ALL
authors of submission at revision stage**

[PAIN_eCopyright_Transfer_Form-convergence-ig.pdf](#)

[Click here to access/download](#)

**Copyright Transfer Agreement--REQUIRED from ALL
authors of submission at revision stage**
PAIN_eCopyright_Transfer_Form Blyth.pdf

[Click here to access/download](#)

**Copyright Transfer Agreement--REQUIRED from ALL
authors of submission at revision stage**
PAIN_eCopyright_Transfer_Form BHS.pdf

To view the full contents of this document, you need a later version of the PDF viewer. You can upgrade to the latest version of Adobe Reader from www.adobe.com/products/acrobat/readstep2.html

For further support, go to www.adobe.com/support/products/acrreader.html

Please wait...

If this message is not eventually replaced by the proper contents of the document, your PDF viewer may not be able to display this type of document.

You can upgrade to the latest version of Adobe Reader for Windows®, Mac, or Linux® by visiting http://www.adobe.com/go/reader_download.

For more assistance with Adobe Reader visit <http://www.adobe.com/go/acrreader>.

Windows is either a registered trademark or a trademark of Microsoft Corporation in the United States and/or other countries. Mac is a trademark of Apple Inc., registered in the United States and other countries. Linux is the registered trademark of Linus Torvalds in the U.S. and other countries.

Please wait...

If this message is not eventually replaced by the proper contents of the document, your PDF viewer may not be able to display this type of document.

You can upgrade to the latest version of Adobe Reader for Windows®, Mac, or Linux® by visiting http://www.adobe.com/go/reader_download.

For more assistance with Adobe Reader visit <http://www.adobe.com/go/acrreader>.

Windows is either a registered trademark or a trademark of Microsoft Corporation in the United States and/or other countries. Mac is a trademark of Apple Inc., registered in the United States and other countries. Linux is the registered trademark of Linus Torvalds in the U.S. and other countries.