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

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1 **1. Introduction**

2
3 Many strategies may guide improved pain treatment. Among these are: 1) translational research
4 (e.g. clinical trials of novel therapies emerging from basic science); 2) population research (e.g.
5 identify pain burden-pain care health service gaps and describe treatment harms); and, 3) primary
6 care research (e.g. describe patient presentation/referral patterns, treatment preferences/goals,
7 develop patient care models/pathways). As in Figure 1, convergence of these strategies can help
8 determine who needs treatment, whether treatments are effective, and how to administer
9 treatments.
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12 Evidence from randomized controlled trials (RCTs) guides early implementation of new treatments
13 and represents the translational link between preclinical research and patient care
14 [25,30,55,65,99]. Controlled phase 1, 2 and 3 RCTs demonstrate safety and efficacy to justify
15 marketing approval of new treatments [23,34,36,98,100]. Knowledge synthesis of multiple RCTs of
16 a treatment, e.g. systematic reviews and meta-analyses, facilitates evidence-based clinical
17 decisions [1,59,64]. “Evidence-based medicine” facilitates treatment selection based on
18 consideration of all available safety and efficacy evidence, sometimes including non-controlled
19 studies and expert opinion [29,40,43,80].
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23 The narrow focus of phase 1-3 RCTs necessitates additional, larger, phase 4 post-marketing studies
24 for safety and efficacy evidence in broader populations [11,75]. However, even phase 4 studies
25 have limitations in generalizing to widespread use, and post-marketing recognition of problems
26 with anti-inflammatory drugs [47,63] and opioids [21,56] has emphasized important gaps between
27 RCTs and real-world practice [62]. Furthermore, statistically significant efficacy (e.g. treatment-
28 placebo difference) in RCTs sometimes translates to a questionably meaningful effect [24,40,73].
29 Such gaps are related to differences in RCT, versus real-world, conditions and emphasize the need
30 for pharmacoepidemiologic, database-driven and other large cohort population research
31 [38,39,82].
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35 Most patient encounters involve primary care providers [20,86,87,94] and challenges in this
36 setting include recognition/prioritization of chronic pain among other competing clinical problems
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1 [66,94]. Further challenges include identifying safe, cost-effective and evidence-based multimodal
2 interventions [17,31,66] and revising practices in response to emerging evidence [41]. As in Figure
3 2, evaluating a new treatment evolves through stages of translational, population-based and
4 primary care research. This article reviews challenges to implementation of pain treatments that
5 may be overcome with closer integration of 1) population-based, 2) translational, and 3) real-
6 world, primary care research.
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14 **2. Population-based research on chronic pain burden and impact of pain treatment**

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18 Chronic pain is a major contributor to the global health burden of non-fatal disease [9,95]. Pain
19 treatment trials should therefore be implemented as part of a complex set of strategies to prevent
20 and control the population impact of pain. Thus, RCTs can inform both chronic pain prevention but
21 also chronic pain burden reduction. Complementary to RCTs, pharmacoepidemiology – the study
22 of the use and effects of drugs in large numbers of people [90] – is characterized by various
23 epidemiological methods, study designs, and data sources to examine patterns of medication use
24 and associated population impact. This impact is broadly defined to include benefits and the
25 harms of medicine use across different population levels (individuals, communities, and
26 population as a whole).
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38 Also, a population perspective may identify evidence-burden gaps in existing trials, and future
39 questions where evidence is most needed. For example, chronic pain prevalence is associated with
40 ageing and analgesic use is common in older (e.g. >65 years old) patients [49], yet this population
41 is commonly excluded from RCTs [6]. Another critical gap in the generalizability of pain RCTs is the
42 recognition that a substantial number of people with chronic pain have multiple pain etiologies
43 and anatomical pain sites, as well as other coexisting multimorbidities [74] that often exclude
44 them from classical RCTs with tight exclusion criteria. These well-recognized problems for RCTs –
45 in many areas – reveal a limited understanding of drug-drug, and drug-disease interactions
46 relevant for older, multimorbid populations on multiple medications and require future study.
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1 As evidence of an important evidence-burden gap, a recent analysis compared registered RCTs
2 within 27 disease groupings against burden of disease data across seven global regions [3]. This
3 study found a widespread mismatch between trials and disease burden for musculoskeletal
4 conditions in all income level strata. Furthermore, other differences – with respect to pain
5 prevalence and treatment – in sex/gender [51], race/ethnicity [14;33] and comorbidities [74]
6 suggest other important evidence-burden gaps in real-world pain treatment and research.
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14 Thus, evidence suggests a mismatch between trials and population pain burden, and that closer
15 alignment between RCTs and population-focused studies would better contribute to chronic pain
16 prevention and control at a population level.
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22 **3. Methodology of translational RCTs and barriers to their implementation into clinical practice**

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24 A prototypical design for a phase 3 trial involves parallel randomization of participants to two or
25 more treatment arms including: 1) the study treatment, 2) a placebo control, and 3) a different
26 dose of the study treatment, or a different treatment comparator [25,96]. A major trial design
27 focus is internal validity (e.g. precision and accuracy), and minimization of bias, requiring random
28 allocation of participants to treatment group, blinding of participants and researchers to
29 treatment allocation, and other important factors including sample size, treatment duration, and,
30 duration/completeness of outcome follow-up [1,48].
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40 Broadly, RCTs, which are diverse in design and purpose, collectively strive for internal validity (e.g.
41 assay sensitivity), external validity (e.g. generalizability), risk-benefit evaluation and cost-benefit
42 evaluation (Figure 3). However, RCTs vary depending on the purpose and research question. An
43 important dichotomy articulated by Schwartz and Lellouch, was between an ‘explanatory’ trial –
44 aiming to demonstrate a biological principle – versus a ‘pragmatic’ trial – aiming to guide
45 treatment choices [83]. This dichotomy remains relevant with divergent purposes such as: 1)
46 industry-sponsored RCTs to demonstrate safety and efficacy to support marketing a new
47 treatment; and 2) ‘academic’ RCTs of available treatments to inform best practices. Explanatory
48 trials – commonly product development trials scrutinized by regulatory agencies – focus on
49 feasibility, internal validity and *assay sensitivity* (ability to distinguish an effective treatment from
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1 a less effective or ineffective treatment) [26]. Pragmatically oriented trials emphasize clinical
2 importance of outcomes and treatment differences as well as generalizability (external validity)
3 [24,76,77,97]. In new treatment development, 'phase 3', confirmatory trials inform the decision to
4 market the product [23,34,36,98]. Fairly recently, the PRECIS-2 tool was validated for the purpose
5 of guiding the design of clinical trials along a continuum from "very explanatory" to "very
6 pragmatic" [61]. In this paper we mostly focus on RCTs of pharmacological pain therapies, as this is
7 where most of the evidence currently exists. However, the principles and challenges discussed
8 generally also apply to trials of nonpharmacological approaches, including multimodal,
9 interdisciplinary management [52;53], which generally require more complex study designs [8;57].
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11 RCTs need a study population sufficiently homogeneous to facilitate recruitment efficiency and
12 maximize assay sensitivity; yet sufficiently broad and generalizable. Barriers to RCT generalizability
13 [76,77] include trials conducted in populations with different socio-demographic characteristics
14 different from the target healthcare setting, , or in healthcare systems with different access or
15 health insurance criteria. Further, the use of participant selection criteria that exclude important
16 patient subgroups or comorbidities limits applicability of findings. Major psychiatric disease [93],
17 cognitive dysfunction [81], and substance use disorder [70] are some examples of patients that
18 might be problematic in a trial (e.g. risk of unreliable/incomplete data), but who would benefit
19 from relevant evidence in clinical practice. Thus, consideration is needed on how to conduct trials
20 in complex and high pain burden patient populations [28]. Here, there may be a role for pragmatic
21 trials, conducted in real-world practice, with populations that represent those at whom the
22 intervention is targeted (e.g. co-existing conditions, primary care setting). Some of these issues of
23 external validity and applicability to real-world practice may be addressed with relatively novel
24 pragmatic trial designs [32,78] such as: 1) a cluster randomised trial design whereby study
25 interventions are randomized at the level of the practitioner, or healthcare institution – instead of
26 at the level of the patient [20]; 2) an enriched enrolment randomised withdrawal design, which
27 include only those who tolerate and respond to the treatment [37; 68]; and, 3) a stepped wedge
28 design – a cluster design whereby all participants eventually receive the intervention [46].
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1 Selection of trial outcome measures is also critical [22,35,50,91,92]. In 2003, the “IMMPACT”
2 group of authors (impact.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].
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7 Since most novel pain therapies have demonstrated efficacy in preclinical models of nociception
8 and pain [34], it is logical that pain intensity be used as a primary outcome measure. However, in
9 practice, pain management does not always result in substantial reductions in pain intensity. This
10 may be due to limited treatment efficacy, dose-limiting treatment side effects, or, analgesia-
11 related increases in physical activity that subsequently increase pain. Despite this, pain
12 management may result in other benefits including improved coping, physical function, mood and
13 sleep even if pain intensity reduction is not always apparent. In this regard, it is interesting to note
14 recent evidence suggesting that the use of a composite outcome measure of both pain intensity
15 and physical function may facilitate improved assay sensitivity of chronic pain RCTs [52] and so,
16 perhaps trials need not rely exclusively on pain intensity as a primary outcome measure. Thus,
17 evidence from trials, reportedly ‘positive’ for the primary outcome of pain intensity, should be
18 carefully evaluated with respect to other secondary outcomes (e.g. function, mood, sleep) [71]
19 and important adverse effects to put the treatment in appropriate clinical context for real-world
20 practice [73]. In terms of treatment safety, evidence emphasizes the need to improve assessment
21 and reporting of treatment-emergent adverse effects in pain trials [88,89], and further, to consider
22 emerging population-based evidence of potential treatment-related harms of currently used pain
23 treatments [21,47,56,63].
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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
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1 an NNT of 7.2 for neuropathic pain in a recent systematic review [31], but Moore et al [67]
2 demonstrated its use in a trial involving 200 people with fibromyalgia in which the range of relief
3 obtained was 0 to almost 100%. Their message was, “Expect analgesic failure; pursue analgesic
4 success” – in other words, even when a drug’s NNT, based on high quality trials, is high, there is
5 still a chance of success with its use in individuals, so long as careful follow-up and early review
6 empowers its cessation in the event of insufficient pain relief [67].
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14 Further translation of trial-based evidence into real-world practice requires input from multiple
15 disciplines as proposed by the GRADE (Grading of Recommendations Assessment, Development,
16 and Evaluation) process. GRADE integrates quality of evidence, balance between beneficial and
17 adverse effects, consideration of patient/public values and preferences and related use of
18 resources [4,5,42]. For example, the IASP Neuropathic Pain Special Interest Group conducted a
19 review of neuropathic pain pharmacotherapy involving systematic review and meta-analysis of
20 treatment-specific trials, GRADE assessment and, ultimately, treatment recommendations [31].
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30 **4. Implementation of research evidence into real-world, primary care, chronic pain management** 31 **and research strategies** 32 33 34 35

36 Due to the need for a comprehensive assessment and differential diagnosis of a presenting pain
37 complaint, primary care physicians are commonly one of the first healthcare providers to evaluate
38 an emerging chronic pain condition and to initiate early treatment approaches. Primary care has
39 been defined as ‘first-contact, accessible, continued, comprehensive and coordinated care’ [101].
40 It is characterized by numerous, brief appointments between patients and multi-disciplinary
41 healthcare professionals led by general practitioners. A primary care consultation (typically 10
42 minutes) is multi-factorial and restricted by the short time available [72]. Thus, ready access to
43 evidence about treatment interventions is essential to effective primary care – particularly
44 relevant to pain management, which accounts for 22% to 50% of primary care consultations (while
45 only 0.3% to 2% with chronic pain are referred to specialist pain clinics) [86]. Recognition of time
46 constraints and patient complexity has encouraged a medical model with prescribed medicines,
47 which are straightforward to implement, and meet the apparent needs or expectations of both
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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
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Although efforts to improve implementation of, and access to, nonpharmacological pain treatments are expanding, the current reality is that analgesic drug prescribing remains one of the most common examples of pain management in primary care settings. Safe and effective analgesic prescribing requires careful discussion and frequent review, often with slow titration to appropriate effective and tolerated doses. This is difficult to achieve with traditional physician-led primary care. Alternative models of care are therefore required, including non-medical prescribing, nurse- or pharmacist-led pain clinics, and shared decision support systems.

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

As alluded to above, lessons learned from the opioid crisis have emphasized the potential value of expanding implementation and access to nondrug treatments for pain as well as pain management team leadership to also involve a broader range of health professionals. In fact,

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

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18 This review highlights barriers to the implementation of RCT evidence into patient care. At a
19 population level, continued efforts to identify various populations with high pain burden should be
20 coupled with new RCTs involving comparable, high pain burden, populations. Given the short
21 duration of RCTs, more pharmacoepidemiologic studies are needed to describe harms with long-
22 term, real-world, use of pain treatments, often used differently than they were in RCTs.
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30 Challenges of treating pain in patients with comorbid conditions (e.g. depression, substance
31 abuse, dementia) – that are commonly excluded from traditional RCTs – suggest a need for trials
32 that feasibly include such complex patients. Other future improvements require RCTs to focus on
33 populations with greater pain burden through careful attention to patient factors such as
34 sex/gender, age, race/ethnicity, socioeconomic status, geographical location and access to
35 healthcare.
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44 Implementing trial evidence into primary care requires expansion of resources, including a
45 broader range of health professionals, to effectively replicate treatment conditions followed in
46 RCTs. Further implementation success requires synthesis and translation of evidence into
47 treatment guidelines, patient care pathways and community-oriented treatment strategies in the
48 context of multimodal therapy.
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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

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

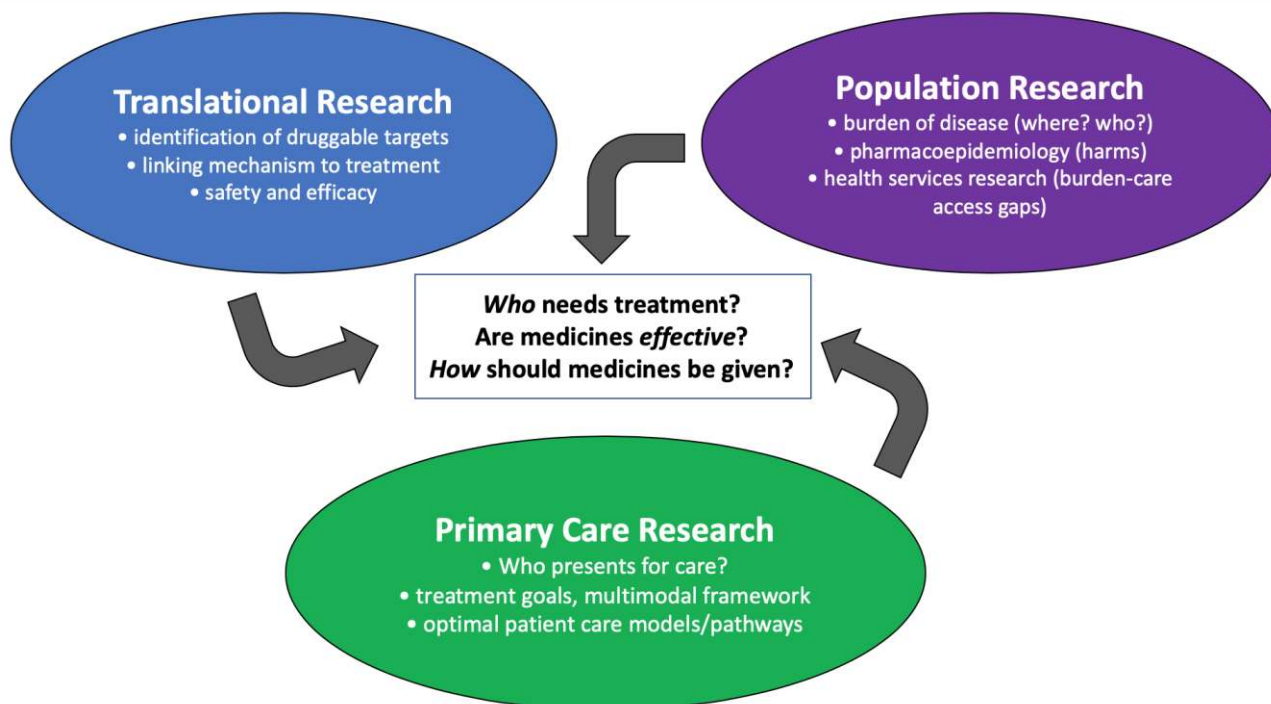


Figure 2: Evolution of the implementation of pain treatments in primary care

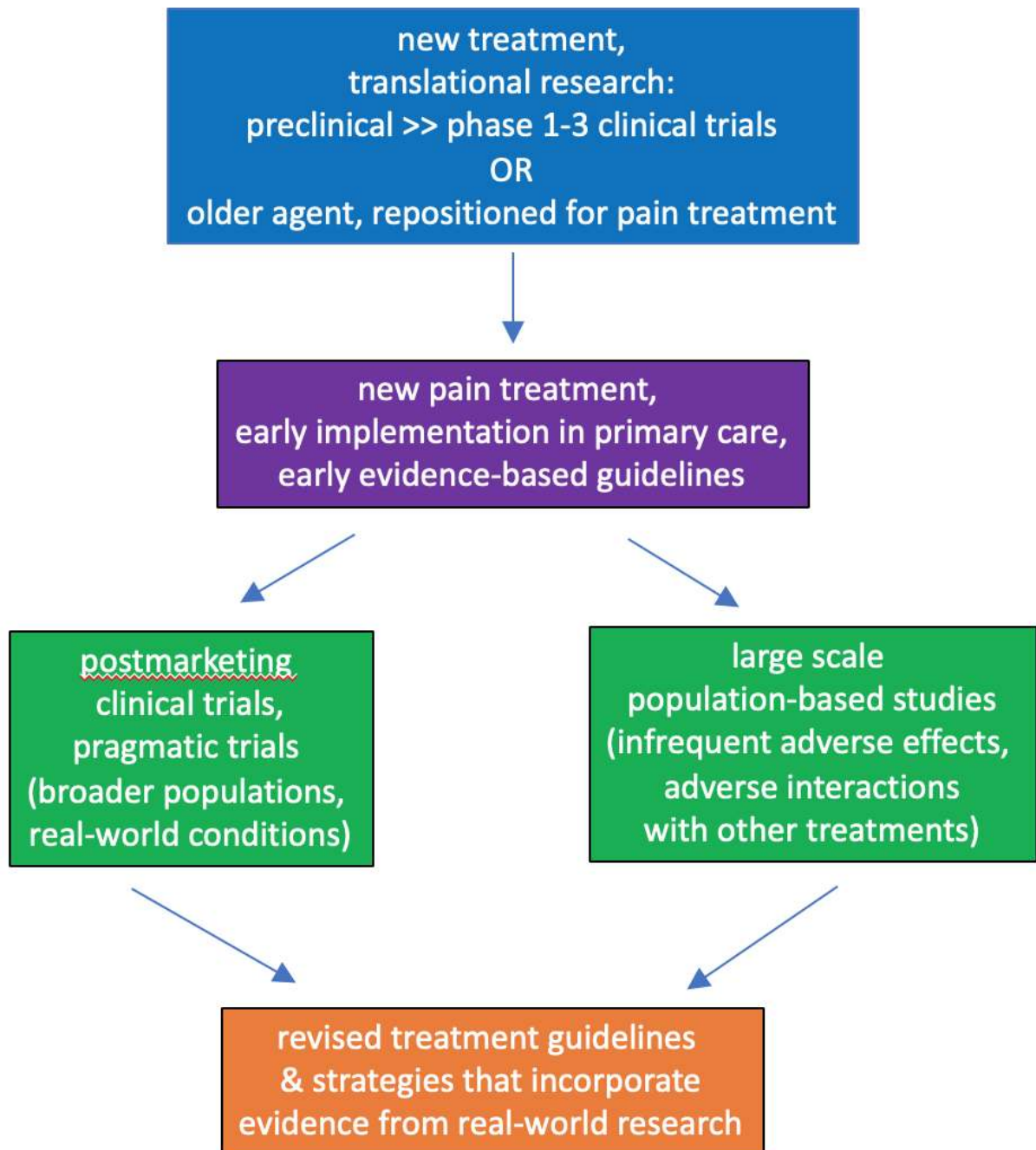
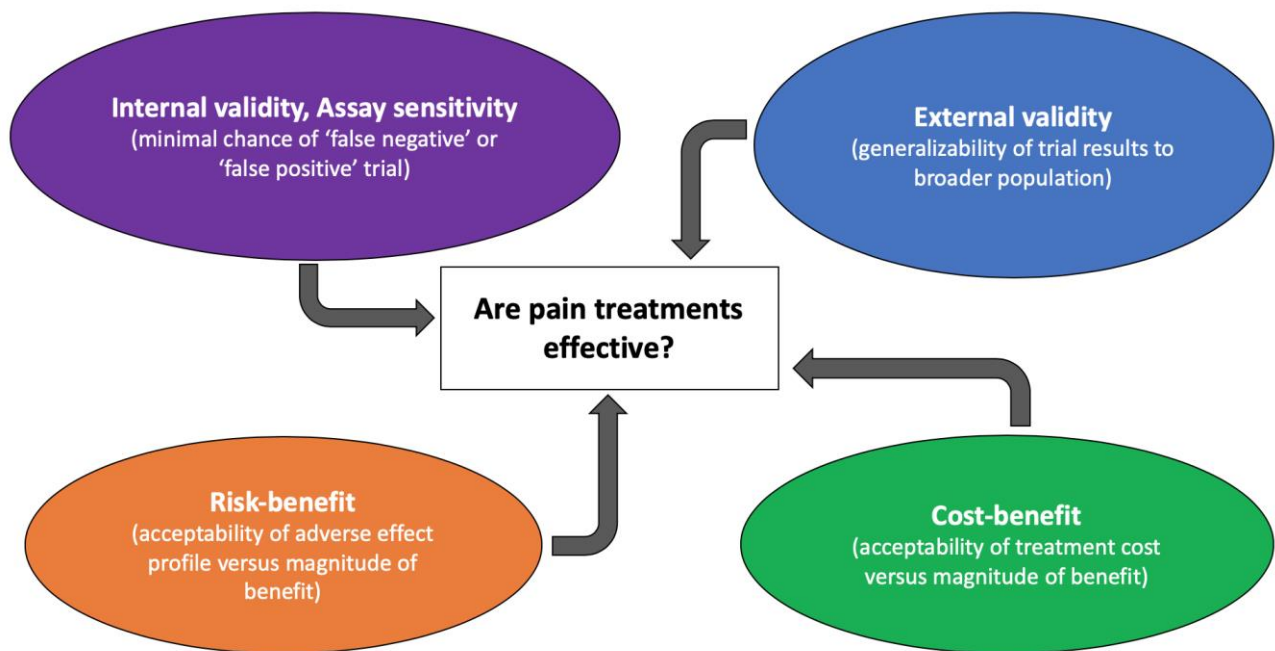


Figure 3: Concurrent goals of clinical trials in the evaluation of chronic pain treatments





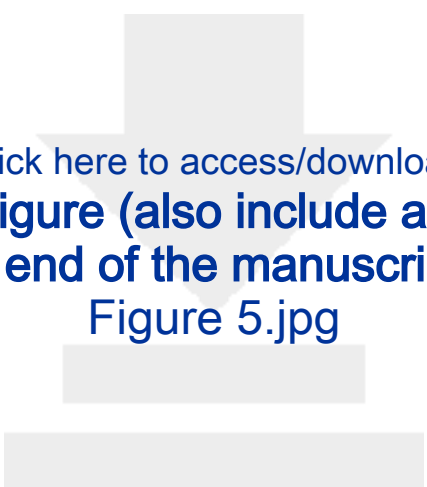
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