Designing and conducting proof-of-concept chronic pain analgesic clinical trials
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Abstract
Introduction: The evolution of pain treatment is dependent on successful development and testing of interventions. Proof-of-concept (POC) studies bridge the gap between identification of a novel target and evaluation of the candidate intervention’s efficacy within a pain model or the intended clinical pain population.

Methods: This narrative review describes and evaluates clinical trial phases, specific POC pain trials, and approaches to patient profiling.

Results: We describe common POC trial designs and their value and challenges, a mechanism-based approach, and statistical issues for consideration.

Conclusion: Proof-of-concept trials provide initial evidence for target use in a specific population, the most appropriate dosing strategy, and duration of treatment. A significant goal in designing an informative and efficient POC study is to ensure that the study is safe and sufficiently sensitive to detect a preliminary efficacy signal (ie, a potentially valuable therapy). Proof-of-concept studies help avoid resources wasted on targets/molecules that are not likely to succeed. As such, the design of a successful POC trial requires careful consideration of the research objective, patient population, the particular intervention, and outcome(s) of interest. These trials provide the basis for future, larger-scale studies confirming efficacy, tolerability, side effects, and other associated risks.

Keywords: Pain, Proof-of-concept, Clinical trial, ACTTION, Quantitative sensory testing, Pain testing, Personalized medicine

1. Introduction
Advances in pain treatment depend on successfully transforming breakthroughs in basic research to new evidence-based treatment strategies. The journey from identifying a novel target to bringing a drug to the market, or development of a novel treatment approach, is intensive, extensive (10–15 years), and expensive (hundreds of millions of dollars). The path starts with basic science studies to identify a target, validate the biologic mechanisms of the target, and find a chemical that appropriately modifies the target. This is followed by preclinical studies in animal models to evaluate the drug’s safety, efficacy, and potential toxicity. The final critical step includes clinical trials in humans to evaluate the candidate drug’s safety and efficacy in a targeted patient population and confirmatory trials to obtain regulatory approval for its use (see Table 1 for a summary of different phases of clinical trials). Although the most common application of proof-of-concept (POC) studies in pain is for the testing of new drugs, these studies have also been used to identify pathophysiological mechanisms of pain in volunteers and individuals with select pain states and to validate new pain "models" and outcome measures in humans. Such studies enhance the pain research toolbox and can lead to new insights into the mechanisms and treatment of chronic pain. History suggests that this complex process is a risky endeavor because few new targets identified for pain therapy by preclinical research have led to successful treatments in clinical practice.

A critical step in reducing risks during the translational process of advancing scientific discoveries into treatments is a well-constructed POC study. In contrast to phase 3 clinical trials that are aimed to evaluate a candidate treatment’s benefit and safety profile in a specific patient population, POC studies are considered early-stage clinical trials performed to determine whether a treatment (eg, drug) interacts appropriately with its molecular target to achieve sufficient biological activity in humans. Proof-of-concept trials are usually designed to include fewer participants for a limited duration of follow-up and are an essential component of the development phase that helps decide
whether to proceed to more comprehensive and expensive phase 3 clinical trials ("go/no-go" decision). They provide initial evidence for target use in a specific population, the most appropriate dosing strategy, and duration of treatment. A significant goal in designing an informative and efficient POC study is to ensure that the study is safe and sufficiently sensitive to detect a preliminary efficacy signal (ie, a potentially valuable therapy). Proof-of-concept studies help avoid resources being wasted on targets/molecules that are not likely to succeed. However, design of POC studies must have sufficient precision and assay sensitivity to ensure that a potentially successful treatment candidate is not inappropriately abandoned, eg, due to inconclusive results from a poorly designed trial.

2. Research questions for proof-of-concept trials

Proof-of-concepts generally provide the first opportunity to ask a research question in patients with various chronic pain conditions, and the nature of the research question will determine the selection of various trial design characteristics. Important differences from POC trials for acute pain treatments include clinical setting (eg, in-hospital postsurgical setting vs outpatient chronic pain clinic), patient population (eg, surgical patients vs patients with chronic disease), and duration of treatment (eg, hours to days vs weeks to months), and these differences have an important impact on various trial design features. From an analgesic drug development perspective, POC trials may be used to provide a preliminary evaluation of the safety and efficacy of

| Phase | Primary goals | Number and type of participants | Time frame | Drug dosing | Notes |
|-------|---------------|---------------------------------|------------|-------------|-------|
| 0: “Exploratory” | To gather preliminary data on pharmacokinetics. To determine whether drug behaves as expected in humans based on preclinical studies. | 10–15, healthy volunteers | Days to weeks | Subtherapeutic ("microdosing") | An exploratory study involving limited human exposure to the drug, with no therapeutic or diagnostic goals. Also known as first in-human trial, sometimes skipped or combined with phase 1 studies. |
| 1*: “Safety” | To determine safety and pharmacokinetics of a range of doses in healthy volunteers. | 20–80, healthy volunteers, or target patient population for drugs that are highly toxic or can only be used in narrowly defined groups (eg, cancer patients) | Days to weeks | Subtherapeutic to therapeutic range | Study the drug’s most frequent and serious acute adverse effects with increased dosage and, often, how the drug is metabolized and excreted. *Subclassified as single ascending dose (phase 1a) and multiple ascending dose (phase 1b). Approximately 70% of drugs move to the next phase. |
| 2*: “Biologic activity” | To establish proof of concept that medication has biologic activity. To further evaluate a drug’s safety in patients. To establish a drug dose and frequency. | 100–300, Patients with specific diseases | Weeks to months | Therapeutic | Data from this phase used to refine research questions, develop research methods, and design new phase 3 research protocols. Studies may not be large enough to confirm drug efficacy. *May be subcategorized as pilot studies designed to demonstrate clinical efficacy or biological activity (phase 2A), and dose-finding studies to determine the optimum dose at which the drug shows biological activity with minimal side effects (phase 2B). Approximately 33% of drugs move to the next phase. |
| 3: “Efficacy” | To confirm drug efficacy and effectiveness, and to monitor side effects. | 300–3000, Patients with specific diseases | Months to years | Therapeutic | Usually drug is compared with commonly used treatments or placebo. Sometimes known as “pivotal” studies. Approximately 25%–30% of drugs move to the next phase. |
| 4: “Postmarketing,” “confirmatory” | To provide surveillance and additional information on treatment or drug’s risks, benefits, and best use after the drug is approved for human use. | Several thousands, patients treated with drug by physicians | At least 2 years | Therapeutic | Monitors the drug’s use in public, often an ongoing process during the drug’s lifetime of active medical use. May result in changes to drug’s approval, labeling, or use. |

*, most relevant to POC. Adapted from the following sources: https://www.fda.gov/forpatients/clinicaltrials/types/ucm20041762.htm; https://www.fda.gov/forpatients/approvals/drugs/ucm405622.htm; https://www.fda.gov/drugs/resourcesforyou/consumers/ucm143534.htm; https://clinicaltrials.gov/ct2/help/glossary/phase; https://prsinfo.clinicaltrials.gov/definitions.html#StudyPhase; https://www.nih.gov/health-information/nih-clinical-research-trials-you/basics.
a new molecular entity (eg, phase 2 trial) in a target chronic pain population. Proof-of-concept trials may also be useful to address a wide variety of other fundamental research goals, such as the development and validation of new pain-related outcome measures, elucidation of physiological pain mechanisms, identification of biomarkers to predict chronic pain treatment outcomes, assessing safety and preliminary efficacy of focused treatment strategies such as combination therapy, evaluating the utility of therapeutic drug monitoring for chronic pain management, and others.

2.1. Mechanistic studies

Proof-of-concept trials that randomize chronic pain patients to receive investigational or control interventions may be used to study a variety of different mechanisms of pain processing and/or analgesic treatment response. In support of a putative mechanism-specific response to analgesic treatment, a number of POC trials have evaluated treatment response according to pretrial pain phenotypes such as painful response to topical capsaicin or a “hypersensitivity phenotype” based on quantitative sensory testing (QST), suggestive of sensitized or irritable nociceptors. Some of these studies have demonstrated phenotype-specific differences in treatment response lending support to the concept of mechanism-based pain treatment. Other POC trials have made use of various techniques and biomarkers, such as functional brain imaging, and genetic analysis, to understand interactions between mechanisms of pain processing and pain treatment outcomes.

2.2. Development of new analgesic treatment strategies

For the purposes of developing a new analgesic treatment, POC trials may use results from earlier phase 1 trials (eg, in healthy human volunteers) to guide the evaluation of safety, preliminary analgesic efficacy, and dose–response of a proposed new intervention in patients with chronic pain. For example, early phase 1 human trials of novel agents such as the glycine antagonist, GV196771, and the AMPA/kainate antagonist, LY293558, led to subsequent POC trials in peripheral neuropathic pain and migraine, respectively. As discussed later in this review, various trial features that are attractive at the POC stage are those that maximize the sensitivity and specificity for detecting analgesic efficacy in the investigational treatment. Further exploration of dose–response in terms of preliminary analgesic efficacy and adverse events may also be accomplished in POC trials beyond what was previously described in phase 1 trials.

The treatment comparator or control interventions, if any, should be carefully considered in POC trials and may include placebo, an alternative active comparator, or a lower dosage of the investigational treatment. Use of a placebo that is otherwise identical matched but devoid of specific biological effect is critical in quantifying the analgesic effects that are specific to the investigational treatment, that is, beyond any nonspecific effects that may be related to patients’ treatment expectations, natural history of the pain condition, and/or regression to the mean (eg, patients with fluctuating pain levels may be more likely to enroll in a trial when pain levels are highest). Placebos are considered ethical as long as trial participants understand that they may withdraw from the trial at any time to pursue other pain treatment and/or that certain rescue analgesic treatment will be provided during the trial, so it is important to understand that these provisions may place limitations on analysis and interpretation of study findings. With respect to evaluating treatment safety in early POC trials, as well as in other types of trials, it should be recognized that participants treated with placebo might also report “nocebo” effects (ie, adverse symptoms or responses that may be attributable to negative expectations about the treatment or its side effects). The inclusion of an active comparator with previously proven efficacy in a POC study of an investigational treatment can serve to confirm “assay sensitivity” by demonstrating a statistically significant difference between the active comparator and placebo in situations where the study treatment fails to separate from placebo, thus failing to demonstrate efficacy. Aside from evaluating novel monotherapies, POC trials have also been useful to evaluate the added benefits of combining known treatments for chronic pain. In this regard, several POC trials have carefully compared analgesic combinations to their respective monotherapies, and several of these have guided subsequent, larger, industry-sponsored trials.

3. Human experimental and clinical models of pain

A successful POC trial requires an appropriate patient population or model disease state. In clinical practice, chronic pain patients often present with a mixture of pain types, as well as psychosocial and cognitive factors, that defy easy classification and characterization of pain. Moreover, many of these patients have other medical conditions that may affect tolerability and response to potential treatments. As a result, inclusion of “typical” pain patients for small-scale clinical trials may make it difficult to demonstrate a true response to an experimental therapy. The use of experimental and clinical models of chronic pain allows for initial identification and definition of an appropriate target patient population (ie, with clearly defined characteristics) and clearer interpretation of experimental findings for specific populations, thus guiding future confirmatory trials.

3.1. Experimental models

Human experimental models of chronic pain have been used to test potential therapies through induction of reversible, experimentally induced pain. The ideal experimental pain model produces reversible or transient pain, does not cause long-term tissue damage or injury to the subject, is easy to perform, and provides reproducible results. The use of experimentally evoked pain models in healthy volunteers can be particularly useful when the target population is small, and it would be difficult to study an adequate number of patients, or when the safety of the therapy is not yet established and testing in patients with medical comorbidities would be inadvisable. Volunteer preclinical studies have a standardized intervention that minimizes variability of the injury stimulus across participants, tend to facilitate recruitment, are simpler to perform, and easier to replicate than patient studies. However, there is ongoing debate as to whether preclinical experimental models in humans are useful in predicting efficacy in patients with specific chronic pain conditions, especially since both the duration of pain and the test of drug treatment effects are brief.

One of the earliest and most commonly used preclinical models of pain is the burn injury model, in which cutaneous heat injury produces thermal and mechanical hyperalgesia in the area of the burn, as well as mechanical hyperalgesia in the surrounding area. This model has been widely used to characterize the analgesic effects of numerous drugs, including...
morphine,15 lidocaine,33 ketamine,87 and ibuprofen130 in healthy participants. However, sensory changes produced by the burn injury model are known to diminish over the course of minutes to hours, and skin injury such as blistering and skin pigmentation changes may occur.130 Thus, investigators should be cautious when considering this method, and participants should be fully informed of the potential risks and consequences (as they should for all testing procedures). The brief thermal sensitization model also produces an area of thermal and mechanical hyperalgesia by delivering a 5-minute, 45°C stimulus to the thigh and measuring the area of hyperalgesia during the last 2 minutes of stimulation.177 This model is likely a better candidate in human studies because it is less likely to cause blistering and readily repeatable. In one report, brief thermal sensitization was performed twice daily for 5 consecutive days with no skin reactions132).

Another common experimental pain model involves the intradermal, intramuscular, or topical application of capsaicin.149 The administration of capsaicin results in acute, transient inflammatory pain the nature, duration, and intensity of which is dependent on route of administration and capsaicin concentration. Like thermal injury, the effects of capsaicin are often brief. The heat/capsaicin sensitization model combines topical capsaicin with thermal stimulation to prolong the ongoing pain and hyperalgesia.23,133 In an area of tissue pretreated with capsaicin, subsequent reapplications of heat can “rekindle” previous primary and secondary hyperalgesia, thereby extending experimental pain duration and intensity while reducing the potential for permanent injury from thermal or chemical burns.

The thermal and mechanical hyperalgesia evoked in the burn and capsaicin pain models, as well as in electrical stimulation

### Table 2
Common experimental pain models.

| Model                        | Type of pain modeled                                   | Advantages                                                                 | Limitations                                                                 |
|------------------------------|--------------------------------------------------------|-----------------------------------------------------------------------------|----------------------------------------------------------------------------|
| Brief thermal sensitization  | Inflammatory/nociceptive                               | Noninvasive Less intense than burn injury model                             | Short duration of pain (min) May not have as strong test–retest reliability as burn injury model or heat/capsaicin sensitization model |
| Burn injury                  | Inflammatory/nociceptive                               | Noninvasive Easily and reliably induced                                      | Short duration of pain (min) Risk of skin injury (blistering and hyperpigmentation) |
| Capsaicin application        | Nociceptive/neuropathic                                | Noninvasive Does not require specialized equipment (e.g., thermodes, electrical stimulators, etc.) | Pain slowly ramps up over time (15–25 min) Wide interindividual variability in response to capsaicin |
| Conditioned pain modulation  | Descending pain inhibition                             | “Dynamic” pain model may be more responsive to treatment May tap into endogenous opioid “tone” | Requires staff training Requires having 2 stimuli available for testing |
| Esophageal stimulation       | Visceral                                               | Most commonly used visceral pain model Accessible for direct visualization and administration of stimuli | Relatively invasive Risk of esophageal injury |
| Heat/capsaicin sensitization | Neuropathic                                            | Noninvasive Decreased risk of thermal or chemical injury to tissues compared with either technique alone Strong test–retest reliability Longer duration of pain (hours) Can obtain more “objective” measures (area of flare and secondary hyperalgesia) | Wide interindividual variability in response to capsaicin |
| Nociceptive flexion reflex   | Spinally-mediated nociception                           | Noninvasive More objective (based on EMG recordings)                        | Requires specialized equipment Short duration of pain Wide interindividual variability Unclear clinical relevance |
| Temporal summation           | Central/pain facilitation                             | “Dynamic” pain model may be more responsive to treatment Mechanical or thermal models available | Thermal devices are expensive, fickle, and mostly not portable Requires staff training |
| Ultraviolet B (UVB) irradiation | Inflammatory                                          | Noninvasive Longer duration of pain (hours)                                 | Onset latency of several hours Peak pain ~24 hours after exposure |
techniques, are intended to correlate with features of neuropathic pain, although they also share features with nociceptive/inflammatory pain. Ultraviolet B (UVB) irradiation applied to small areas of skin produces stable mechanical and thermal hyperalgesia as a model of inflammatory pain. Visceral pain has been modeled in the esophagus using electrical, mechanical (dilation), thermal, and chemical (acid and capsaicin) stimulation, although the level of invasiveness and risk for esophageal perforation limit its use. Other less common modalities have also been used to model chronic pain states, including mechanical (pinch), thermal (freeze lesion and laser), chemical (acids and hypertonic saline), and electrical stimulation, but their roles in translational pain research are not yet well-established.

Experimentally evoked pain models are useful for gathering additional data on safety and tolerability, dose finding, and as early explorations of potential analgesic efficacy or mechanism of action, particularly when a study needs to be completed within a relatively short time frame or has limited access to chronic pain patients. These models’ ability to predict analgesic response has driven considerable interest in recent years, however, it remains premature to suggest the effects of which drugs could be characterized by which testing methods. The selection of an appropriate model depends largely on the type of pain to be investigated and the hypothesized site of action of the treatment, but other considerations include the desired duration of elicited pain, the specific characteristics of the pain treatment to be studied, the resources available to the study team, and the expertise of the investigator. These same issues may also influence the implementation of the chosen experimental model, including the intensity, duration, and location of the pain-evoking stimuli.

When considering the use of experimental pain models, their potential limitations must also be taken into account. Although each of the models described above offers standardized protocols and reproducible results, large interindividual variability has been reported. Potential participants may therefore need to be screened to maximize the likelihood that they will respond as anticipated to the planned pain model. In addition, investigators should recognize that experimental pain models are susceptible to habituation, such that repeated applications of the same painful stimuli in the same participant may elicit less pain over time. Habituation may therefore limit both the duration and frequency of assessment of pain in experimental models.

Experimental pain models are not always the best choice for POC pain trials. For example, experimentally evoked pain does not always respond well to analgesics with established effectiveness, suggesting that these models are not perfectly correlated with specific chronic pain states. One possible explanation is that many pain treatments require repeated or prolonged administration of medication to detect benefit, and the nature of laboratory models does not allow for long-term assessment of therapy. Another major limitation of these models is that study participants typically do not have chronic pain, and acute injury may not accurately reflect the numerous physiologic and psychological changes that occur with chronic pain. In addition, although some experimental models create temporary central sensitization with a definable area of secondary hyperalgesia, researchers cannot ethically induce an actual, potentially long-term injury to a nerve. A localized pain model in volunteers is unlikely to simulate the multiple complex changes that are associated with a nerve injury in humans.

Consequently, findings in experimentally evoked pain studies may not readily translate to clinically relevant effects in actual chronic pain patient populations. Some researchers have advocated the use of brain imaging modalities to bridge this potential gap between experimental and clinical pain treatment efficacy, but more studies and refinement in techniques are necessary to explore the full potential of neuroimaging in the development of POC trials. As recently reviewed, sensory testing and imaging hold “promise as pain biomarkers and should be carefully considered for possible inclusion when designing clinical trials of pain treatments.” Investigators contemplating incorporating such methods into their trial should consider whether such testing may aid in explaining the hypothesized mechanism of action, optimize the trial in some fashion, or facilitate accelerated progression of intervention development.

3.2. Selected clinical conditions

Proof-of-concept trials designed to assess preliminary signal of treatment efficacy typically evaluate patients with specific, well-defined chronic pain conditions that may serve as “model” pain states, and the results can later be extended more broadly to other related types of chronic pain. Appropriate selected chronic pain conditions should have well-established diagnostic criteria to enhance study uniformity and reproducibility, as well as enough prevalence to allow for adequate enrollment. The most common neuropathic pain conditions studied are painful diabetic peripheral neuropathy (DPN) and postherpetic neuralgia, but other peripheral neuropathic pain states such as HIV-associated neuropathy, post-traumatic neuralgia, lumbar radiculopathy, and chemotherapy-induced peripheral neuropathy have also been studied. Selected conditions of central neuropathic pain include poststroke pain and pain associated with spinal cord injuries. Rheumatoid arthritis is one of the most commonly used selected clinical conditions of inflammatory pain, whereas osteoarthritis has features of mechanical, inflammatory, and even, according to some researchers, neuropathic pain. Fibromyalgia is a classic example of a disorder of central sensitization, in which pain occurs even in the absence of tissue abnormalities.

Unlike preclinical models, clinical conditions of pain demonstrate significant patient heterogeneity, both among and within specific pain conditions. Clinical pain in certain individuals may result from multiple mechanisms, making it more difficult to interpret and apply experimental findings. In addition, placebo group response in pain studies is typically quite high. In a review of neuropathic pain trials, studies with a high placebo response were less likely to demonstrate a positive treatment effect. There is some evidence that placebo group response may be affected by the pain condition studied; for example, placebo group improvement has been found to be significantly higher in DPN compared with postherpetic neuralgia. Thus, it is important to bear in mind the particular characteristics, strengths, and limitations of each potential model during the design and interpretation of POC trials. Models of chronic pain provide an important framework for understanding mechanisms of chronic pain and characterizing pain treatments, and they are a critical aspect of POC study design.

4. Research designs

Successful POC trials require substantial consideration in selecting the most appropriate research design for the particular research question, intervention, and outcome(s) of interest. The Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT) has published several recommendations and
Table 3

| Design                                    | Brief description                                                                 | Advantages                                                                 | Limitations                                                                 |
|-------------------------------------------|-----------------------------------------------------------------------------------|-----------------------------------------------------------------------------|----------------------------------------------------------------------------|
| Parallel group                            | Participants are assigned to 1 of 2 or more different treatment arms<br>“Most commonly used” | Shorter duration (compared with cross-over)<br>No carryover effect<br>Simple<br>Applicable to acute conditions<br>Uncomplicated analyses and interpretation<br>Small study population | Larger sample size (compared with cross-over)<br>Does not take interindividual variability into account |
| Matched pair parallel design: pairs of participants with similar characteristics randomized to different interventions | Can reduce variability from treatment comparison |                                                                           | Slow recruitment<br>Difficult to implement depending on characteristics to match |
| Cross-over                                | Each patient receives each intervention and serves as their own control            | Smaller sample size (allows for within-patient comparison; patient is their own control)<br>Removes interpatient variability<br>Provides strong unbiased estimate for difference between treatments<br>Increased power | Longer (requires washout period and interventions)<br>Carryover effect are possible<br>Must consider order effects<br>Greater patient burden and drop-outs<br>Missing data are more problematic<br>Internal and external factors are assumed constant over time |
| Enriched enrollment randomized withdrawal | Participants that respond to intervention are randomized to continue receiving it or to placebo. Return of symptoms withdraws placebo participants | Minimizes time in placebo condition<br>Can inform how long a treatment should be continued | Carryover effects are possible<br>Longer duration/lag time before randomization<br>Underlying active disease is unclear |
| Sequential parallel comparison design     | Allows for rerandomizing placebo nonresponders to the treatment or placebo in a later stage of the trial | Decreased placebo effect in the second stage (after rerandomization) enriches population<br>Reduces sample size requirements<br>Increases power | Longer duration<br>Patented, must pay to use it<br>Duration may not be stipulated in advance<br>If placebo nonresponders are treatment refractory (and would not benefit from any study treatment), reduces overall power |
| Adaptive                                  | Allows for modifications while trial is ongoing<br>MOST: evaluates factors and conditions through an engineering framework<br>SMART: already collected data informs how and when to modify treatment<br>JITAI: uses mobile technology to assess behavior and deliver tailored treatments in real time | Increased efficiency<br>The safety, efficiency, and efficacy improve over the course of the trial<br>More participants will get assigned to the more successful treatment over time<br>Improved efficacy and efficiency | Extensive consideration required in planning, execution, and interpretation<br>Requires high-level statistical expertise<br>Bias may be introduced by alterations<br>Highly specialized<br>Limits between person generalizability<br>Highly specialized<br>Limits between person generalizability<br>Complications from devices<br>Intense data collection = lots of data<br.Requires specialized statistical abilities |

(continued on next page)
| Design                          | Brief description                                                                 | Advantages                                                                 | Limitations                                                                 |
|--------------------------------|-----------------------------------------------------------------------------------|----------------------------------------------------------------------------|----------------------------------------------------------------------------|
| **Drug-dosing paradigms**      |                                                                                   |                                                                           |                                                                            |
| Single dose                    | Delivery of a single administration of specified intervention that has a prompt onset, often used to characterize PK | Simple                                                                    | Only for rapid onset of action interventions                              |
| **Multiple dose/dose ranging** |                                                                                   | Lower probability of missing data                                         | Effects of repeat applications are unknown                                 |
| Parallel: classic paradigm.     | Patients are randomized to receive one dose (or placebo) for the entire study     | Short duration (depending on follow-up period)                            | Higher cost                                                                |
|                                |                                                                                   | Decreased cost                                                            | Longer duration                                                            |
|                                |                                                                                   | Most common method                                                        | Requires larger sample size                                                |
|                                |                                                                                   | Able to evaluate repeat applications                                     | Less appropriate when the safety profile is unknown                        |
|                                |                                                                                   | Can compare each treatment group with control                             | Consideration must be directed to when a dose will be increased            |
|                                |                                                                                   | Reduces the number of subjects exposed to unsafe or ineffective doses      | Close monitoring of side effects is required as higher doses are administered |
|                                |                                                                                   | May require few subjects                                                   | Individualized treatments are time consuming                               |
| Dose titration: participants    |                                                                                   | Appropriate when a drug is needed for a longer duration                   | May require specialized analyses and interpretation                        |
| increase throughout the study  |                                                                                   | Good for use when dose is likely tailored to a subject’s reaction         | Requires a larger sample size                                              |
|                                |                                                                                   | Appropriate where large individual variability is expected                | Must manage × number of cohorts on differing doses                          |
|                                |                                                                                   | Increases patient safety with fewer participants exposed to each dose     |                                                                            |
| Dose escalation: participants   |                                                                                   |                                                                            |                                                                            |
| start at a low dose,           |                                                                                   |                                                                            |                                                                            |
| a NEW cohort is recruited for   |                                                                                   |                                                                            |                                                                            |
| increasing doses               |                                                                                   |                                                                            |                                                                            |
| Cross-over: see above in-design section |                                                                                   |                                                                            |                                                                            |

| Administration frequency       |                                                                                   |                                                                            |                                                                            |
| Single dose                    |                                                                                   |                                                                            |                                                                            |
| Multiple dose                  | See above in dosing section                                                       | Allows for systemic accumulation                                          | Frequency must be considered                                              |
| Continuous dose                | Repeated administration                                                            | May evaluate effects of repeated application                              | Longer duration                                                            |
|                                | Constant delivery                                                                  | High degree of control over environment                                   | Primarily inpatient                                                       |
|                                | Cross-over: see above in-design section                                            | Confidence in dose “taken”                                                | Requires specialized equipment and training                                 |

* Adapted from Gewandter et al., 2014.

JITAI, just-in-time adaptive intervention.
systematic reviews in recent years that have advanced the field and guided trials to be more cohesive. The group recently published POC consensus recommendations and an overview of research designs; the reader is directed to Gewandter et al. for a more thorough review of each method and detailed strengths and weaknesses of each approach, also briefly overviewed in Table 3. Design options for POC clinical trials are similar to those of larger clinical trials and frequently inform dosing, safety profile, preliminary signal of efficacy, selection of patient population, the specific assessments most meaningful to the population, as well as initial estimate of feasibility, all useful in planning for later phase studies. The most common research design elements used in POC trials are summarized here (Table 3).

### 4.1. Parallel group

Parallel group designs assign participants to one of the multiple treatment groups (eg, active treatment, placebo, and active comparator), and they remain in the assigned group throughout the duration of the trial. This design is particularly useful when drug effects are of lengthy or unknown duration; however, it requires larger sample sizes than cross-over trials (described below). To enhance the comparability of the placebo and intervention treatment groups, stratified randomization with blocking (or a similar technique) is recommended when possible. Blocking enhances balance in terms of the number of subjects allocated to each group. The number of stratification variables should be limited, and they should be variables that are strongly associated with outcome.

### 4.2. Cross-over

A cross-over design is a repeated-measurements (within-subject) design, in which each participant receives more than one different intervention during a specified period (ie, the patients “cross-over” from one treatment to another at a specified interval during the course of the trial). This design typically requires a “wash-out” period of sufficient length between ending one intervention and initiating another. Each participant therefore serves as his or her own control, providing greater statistical power for analyses with fewer participants than parallel group designs. Cross-over designs may yield a lower placebo response when compared with parallel group trials, hypothesized to result from participants receiving both the active and placebo treatments. However, given their temporal nature, cross-over designs are not suitable for treatments that have long-term effects or outcomes that cannot be measured relatively quickly, and particularly when an appropriate wash-out period is unknown or not feasible.

### 4.3. Enriched cohort

Enrichment designs encompass a number of strategies used to increase the likelihood that a drug effect will be detected if it exists. They focus on selecting appropriate participants (1) to decrease heterogeneity, such as selecting patients with specific characteristics to increase power, (2) to display the endpoints of interest (prognostic enrichment), and/or (3) that may be most likely to respond to the intervention (predictive enrichment). Such enrichment designs may improve assay sensitivity and potentially improve the likelihood of detecting patient subgroups that could benefit most from specified treatments, given the attention paid to responders. However, they may not necessarily improve the efficacy or efficiency of a trial (as they may require a longer overall study period to identify responders), may underestimate adverse effects, and could limit generalizability (although limited generalizability is not typically a concern for POC trials).

### 4.4. Adaptive designs

Adaptive clinical trial designs allow for ongoing modifications to the trial based on observations and data generated at specified periods over the extant study period. This flexibility affords opportunities to alter procedural aspects of the study, as well as the statistical plan, after the trial has been initiated but before its completion. Such modern designs improve the efficiency of trials and potentially enhance understanding of treatment effects by allowing incoming data to guide refinement of the trial. For example, inappropriate dose selection is frequently a concern in drug development. An adaptive dose-finding POC trial might include several doses to evaluate dose–response and allocate additional patients to the doses showing greatest initial promise, thereby reducing the number of participants assigned to receive a less ideal dose. Similarly, group-sequential designs incorporate a framework for analyses, as data are collected; analyses are conducted, as data are collected; and continued trial enrollment is based on predefined stopping rules. Sequential parallel comparison designs also allow for rerandomization of placebo nonresponders to treatment or placebo in a later stage of the trial. For example, placebo nonresponders are rerandomized to a second stage where they either receive placebo or active treatment, creating an additional subgroup for analysis and interpretation of true treatment effects. This design specifically seeks to address high placebo response rates, which is particularly relevant for chronic pain studies, and allow for additional data (specifically from placebo nonresponders), increasing the efficiency of the trial.

Despite their potential to improve trial efficiency, adaptive designs have not been widely reported in the extant literature. However, these study designs are gaining attention, and recent nonpharmacological work suggests an important place for them. For example, examining the points at which exposure to a specified intervention should occur or the order in which to introduce various aspects of one or more interventions represent an important and neglected area for nonpharmacological trials, which may be particularly suited to a POC trial. Multiphase optimization strategy (MOST) aims to improve the efficacy and efficiency of behavioral interventions through evaluating discrete factors and combinations of experimental conditions through an engineering framework. Sequential, multiple assignment, randomized trial (SMART) designs exploit collected data to inform decision making regarding how and when to modify a patient’s treatment and may be included in a MOST design. It specifically seeks to optimize time-varying components of an intervention design, for example deciding the best sequence to
deliver a series of intervention components. Limitations include being highly specialized and personal, so between-person generalizability is limited (not necessarily a problem for POC trials). Just-in-time adaptive interventions, perhaps the most cutting-edge clinical trial design, use smart phones, mobile computers, sensors, and software analytics to automatically detect an individual’s behavior and deliver tailored treatment in real time. Although these innovative paradigms are gaining traction in mental health and substance abuse research, they have not yet been applied widely to the field of pain. A handful of pain studies that have applied such methods have focused on adapting stimulation parameters and position of sensors in neuromodulation studies. Expanding the use of adaptive designs and identifying decision rules that can guide the individualized sequence of intervention implementation could improve outcomes and advance personalized pain medicine. Although novel and potentially valuable, adaptive designs do include multiple limitations and practical hurdles. The temporal framework, or how variables of interest interact and are ordered over time and across environments, can be challenging to discern, although strategies such as ecological momentary assessment provide opportunities to evaluate timescale.

4.5. Drug-dosing paradigms

4.5.1. Single dose

Single-dose trials involve delivery of a single administration of the specified intervention, often randomized with placebo, and monitoring of analgesic effects. Single-dose administration is a feature that can be incorporated into a variety of POC trial designs, such as parallel-group, cross-over studies, or cohort studies, discussed above, or even as a smaller study within the context of larger, repeated-dose trials. Such single-dose studies are frequently conducted as an initial step to evaluate safety parameters. In multiple ascending dose trials, patients are administered 2 or more substances with order over, where patients are administered 2 or more substances with dose trial, but outside of the pharmaceutical realm, are emerging. One such study found that healthy participants who underwent a brief, single cognitive-behavioral intervention evidenced reduced areas of secondary hyperalgesia to thermal stimuli compared with a control group. In a mixed etiology chronic pain study, patients were found to benefit from a single, ~2-hour session of cognitive-behavioral therapy for pain catastrophizing, a negative mental set characterized by rumination, helplessness, and magnification of pain sensations. For additional information on psychosocial clinical trials for pain, see “Unique aspects of clinical trials of psychosocial and integrative chronic pain treatments” by Kerns, Edmonds, Turk, and Williams.

4.5.2. Multiple dose/dose ranging

Dose-ranging studies involve administering different doses of an agent and analyzing each to evaluate the most effective dose with the fewest side effects. These include parallel dose comparison studies, where several potential doses are selected and subjects are randomized to receive one of the doses or placebo for the entire study; dose-escalation studies, where a low dose is titrated up incrementally to the maximum tolerable dose, or to the onset of side effects; dose escalation, where a group is administered a starting dose and (when appropriate) a new cohort is recruited and administered a higher dose; and cross-over, where patients are administered 2 or more substances with a washout period, as described above. At predefined points or at the end of each study type, a comparison can be conducted between each treatment group and the control group to examine safety and efficacy. Each method has pros and cons (Table 3).

4.5.3. Administration frequency

Several drug administration regimens are available; single-dose administrations, as described above, multiple and continuous administration are the most frequently used. Repeated administration is the most common medication delivery regimen. In this approach to the maintenance of drug therapy, doses are taken at specific intervals; often desired accumulation occurs when the drug is administered before the previous dose is completely eliminated. The amount of drug within the system progressively rises. Dosing level and frequency are chosen (likely based on single-dose safety studies) to achieve therapeutic systemic drug levels and maintain a steady state, providing an opportunity to allow for monitoring of safety parameters. In multiple ascending dose studies patients receive low doses of the drug, which are subsequently escalated to a predetermined level. A “safety margin” may be determined from such dosing schedules when administered around a therapeutic window: continuous dosing, often continuous infusion, and delivers medication constantly for hours or days. It is most often conducted in cases of post-operative pain, severe cancer pain, or during vaso-occlusive
criterion in patients with sickle cell disease or labor and delivery. These dosing regimens are infrequently conducted in POC trials.

5. Maximizing assay sensitivity in proof-of-concept trials

Providing first evidence of efficacy of a new treatment in a POC trial is facilitated by clinical trial factors that maximize trial assay sensitivity—defined as “the ability of an RCT to distinguish an effective treatment from a less effective or ineffective treatment.”47 Such factors may include (1) evaluating the maximally tolerated dose/intensity of the treatment; (2) using methods that minimize variability in outcome measurement; (3) studying a specific population (eg, postherpetic neuralgia vs a more heterogeneous group of neuropathic conditions); and, possibly, (4) adopting trial features that minimize nonspecific improvements often referred to as “placebo effects” but not necessarily limited to placebo-treated individuals. In the setting of POC trials, a “negative” trial would be considered a trial with an outcome that generates a “no-go” decision (ie, no evidence of analgesic efficacy—no reason to proceed to phase 3), and a “positive” trial would be considered a trial with an outcome that generates a “go” decision (ie, promising evidence of analgesic efficacy—supports proceeding to phase 3). Thus, a key objective of POC trials is to minimize the risk of a “false-negative” trial outcome, or not detecting benefits of efficacious treatments, while also considering the potential tradeoff of having a “false-positive” trial, or finding a benefit, ie, purely an artifact.47,63 Several strategies currently being investigated may help improve assay sensitivity in POC trials and other types of analgesic trials; these include (1) focused training of trial participants to more reliably rate their pain,54; (2) limiting the number of clinical trial sites in multicenter trial with the expectation of reducing the magnitude of placebo response,47; (3) excluding prospective trial participants with highly variable baseline pain levels54; and (4) restricting the use of concomitant analgesic treatments during clinical trials.47

6. Mechanism-based approach to analgesic trials

Confirming the specific target and mechanism of action for an investigational drug, based on preclinical animal data, is often the driving force behind POC trials. Disease-specific preclinical models that hope to reproduce pathophysiological conditions studied in humans have been developed, albeit with variable translational potency.131 However, personalized, mechanism-based treatment, while suggested nearly 30 years ago,14,27,148,153 has been slower to take shape. There has been an increasing recognition in recent years that substantial variability exists between patients, even with the same diagnoses, advancing the call for personalized pain medicine. Predicting the response to pain treatment has become an area of intense interest. This goal would incorporate genetic, demographic, and clinical phenotype information to deliver a specified intervention to those for which it might be most beneficial. Such identification could be used to group patients according to pain-related sensory profiles to enhance pain care. Recent work has outlined a number of recommendations for such profiling.6,50,155 Characterizing psychosocial factors, baseline pain report, within-patient variability in pain perception, underlying pain mechanism, behavioral measures such as sleep and fatigue, response to sensory testing/pain modulation profile, responses to pharmacological challenges, and genetic profile are all targets for population subgrouping. Predictive algorithms for identifying which—or which combination—of these factors might predict intervention efficacy is an exciting study frontier and well-suited for POC trials, given their exploratory nature.

Indeed, increasing attention has focused on predictive phenotyping before some specified treatment, often analgesic trials,49,51,75,125,185 or surgical intervention.177,179,176 Presumably, such profiling could be of great clinical importance to identify target populations for whom the intervention of choice may have the greatest benefit, to recognize likely nonresponders and allocate supplemental resources to them or, in the case of modifiable risk factors, to develop alternate interventions to target the specified characteristics, potentially improving the likelihood of benefit in refractory groups.

6.1. Subgrouping patients

Historically, 50% of randomized clinical trials report at least one subgroup analysis.134 Guidelines have been proposed for evaluating and interpreting the results of subgroup analyses,46 which include evaluating the clinical importance of the difference, whether the hypotheses were stated a priori or were exploratory, whether the subgroups were limited in number, and if repeated, whether there is general consistency across studies.126 Typically, subgrouping is exploratory and should be interpreted with caution; however, unplanned subgroup analyses can be valuable to inform hypothesis generation for future study. Not surprisingly, larger, prospective studies are required to power subgroup analyses appropriately. Recent work has reviewed the challenges of postrandomization subgrouping.40 Although subgrouping at the POC stage should be conducted and interpreted with caution, the study population within a POC trial could be prospectively enriched to include those with the greatest likelihood benefitting.172

Predefining the mechanistic classification of patients to categorize likely responders is a developing area of considerable excitement. Although this manner of deep phenotyping, comprehensively assessing factors of interest, has spurred a number of studies exploring postoperative pain outcomes12,28 and at least one large population-based study to identify characteristics that contribute to the onset and persistence of pain,111 POC and other clinical trials have been slower to use these concepts. Recent IMMPACT meetings have focused on improving assay sensitivity,47 patient phenotyping in clinical trials of chronic pain,50 and on specific viable biomarkers, including sensory testing, skin punch biopsy, and brain imaging, suggesting a number of promising tools for incorporation into clinical trial design.155 Here, we briefly summarize some of the research to date that focuses on baseline characterization of pain mechanisms and their impact on treatment response.

6.2. Genetic profile

The extent to which genetic factors impact patient response to treatment is an area of substantial interest. Identifying the genetic factors that contribute to variability in opioid efficacy, metabolism, and adverse effects will advance personalized pain management, with the future objective of point-of-care genotyping to assist clinicians in personalizing drug-dosing regimen to each individual. Rodent models have produced hundreds of candidate pain genes (http://www.jbldesign.com/jmogil/enter.html), and genetic association studies have evaluated how single-nucleotide polymorphisms are associated with clinical pain and pain sensitivities.159,173 Evaluation of genetic factors and their potential in informing analgesic choice or dosing strategy has been reviewed comprehensively,14,27,36,58,99,119,148,153,166,172 and new studies...
are exploring genetic subgroups in treatment efficacy and safety.135 Generally, genetic association studies examining drug response have not yielded conclusive guidance on treatment. Epigenetic studies may aid in addressing some of the dynamic gene-by-environment interactions that likely play a role in pain generation and chronicity.4,38 Clinical trials designed to include genetic analysis could be extremely useful in patient subgrouping to improve drug efficacy, reduce side effects, and ultimately optimize pain management. Given the smaller sample size of POC trials and the logistics and cost of collecting and processing DNA, such genetic subgrouping can be exploited in POC trials by only including participants with the variants of choice.

Perhaps the most progress has been made in understanding the influence of the drug metabolism pathways, particularly the cytochrome p450 system, on both analgesic efficacy and adverse effects. A small "pharmacokinomic" randomized, cross-over, double-blind, placebo-controlled trial in healthy men found that an individual’s CYP2D6 genotype (categorizing them into metabolizer phenotypes) impacted the relationship between oxycodone dose, expected plasma levels, and the therapeutic range, offering dosing guidelines based on genotype.106 Although this assessment had notable limitations,106,141 it attempts to merge genomic and pharmacokinetics to advance personalized patient care. Similar work has been performed in assessing codeine and methadone.61,96 Another ongoing study in chronic low back pain is seeking to link genetic polymorphisms of cytochrome p450 enzymes and other relevant pain processing molecules, as well as sensory testing responses, to tricyclic antidepressant, opioid agonist, and GABA A-agonist treatment effects.149 Such studies are time- and resource-intensive but necessary as a step toward individualized pain care. Nevertheless, because of the large sample sizes required to elucidate DNA’s contribution to drug response, genetic profiling has limited utility in POC trials until more conclusive work reveals the specific polymorphisms or clusters of single-nucleotide polymorphisms, and potentially interaction with other characteristics, that could modulate treatment effects.

6.3. Sensory phenotypes

The association between various QST measures and clinical pain has been well-documented, both in connection to acute and chronic pain perception, sensitivity in forecasting clinical deterioration, as well as prediction of postoperative pain outcomes in a variety of surgical procedures.32,71,128,175,182–184,186 Emerging evidence suggests that nociceptive characteristics may serve as predictors of response to a number of nonpharmacological interventions including multidisciplinary pain treatment,50 spinal pain outcomes,31 and spinal cord stimulation outcomes.21 Although few clinical trials have taken advantage of this approach,50 academic endeavors suggest promising opportunities.16 Several reviews have recently summarized the utility of QST in quantifying sensory function and its potential value in selecting patients that might be most appropriate for a certain intervention.32,50,73,94,156,160,169,184 In 2013, Grosen et al.75 comprehensively reviewed the extant QST literature specific to predicting response to analgesic treatment.

In brief, baseline QST responses have been associated with the efficacy of lidocaine, lamotrigine, pregabalin, oxycodone, oxcarbazepine, and placebo analgesia.50 In a multicenter observational cohort study, Grosen et al.75 found that opioid response was predicted by cold pain intensity, pain catastrophizing, and beta EEG activity induced by laboratory cold pain in a small sample of mixed-type chronic pain patients. Pretreatment pain inhibition, often measured through conditioned pain modulation (counterirritation believed to reflect descending pain control156), has been associated with postoperative pain outcomes.13,188 the benefits of exercise,106 morphine consumption after chest wall surgery,77 duloxetine benefit in painful diabetic neuropathy patients,182 and NSAIID efficacy.49

Prespecified QST hypotheses have recently emerged in a handful of study designs. For example, some used QST to identify an “irritable nociceptor” subgroup, or sensory hyperexcitability, and evaluated whether the specified intervention had differential efficacy based on this group membership.7,22,37,38 This concept is nicely illustrated by Demant et al.,38 who observed greater analgesic efficacy of oxcarbazepine for neuropathic pain in an “irritable nociceptor” sensory phenotype subgroup, determined through comprehensive QST battery to identify those with sensory gain, vs no efficacy in the “nonirritable nociceptor” subgroup. Such subclassification of patients at baseline has produced excitement but has been met with mixed results in other clinical analgesic trials.22,35,37,83,93,110 As recently discussed by Dworkin and Edwards,44 these studies contain important methodological differences, including assessment of a single active treatment, comparison between active and placebo interventions, and retrospective analyses, so the exact role of QST in guiding study design and treatment decisions has yet to be firmly established. Nevertheless, these findings show promise in eventually elucidating QST-identified, shared underlying pain mechanisms that would impact treatment response and/or selection of advantageous subgroups, but the vast heterogeneity of conditions, outcomes, and QST methods have proved challenging in moving routine QST characterization into trials.169

6.4. Psychobehavioral profile

Psychosocial and behavioral characteristics and how they may impact treatment outcomes have been reviewed recently with recommendations for including specific measures in clinical trials.50 A few more recent studies continue to advance such assessment. In an evaluation of postoperative opioid consumption after hysterectomy, Janda et al.88 found that, after controlling for other potential predictors, a 1-point increase in fibromyalgia survey scores (based on the 2011 criteria) were associated with an increase of 7-mg oral morphine equivalents. Interestingly, those scoring in the top third of the survey required nearly 30% more opioids than those scoring in the bottom third. These findings replicate previous work, finding that fibromyalgia survey score predicted enhanced opioid requirements after total knee and hip arthroplasty.18 In an elegant series of studies, Booth et al. identified 3 questions, answered before cesarean delivery, that predicted postcesarean evoked pain.129 These questions included assessment of anxiety and anticipated pain level and analgesic use. In a subsequent study, the investigators randomized patients endorsing elevated risk for postoperative pain, based on responses to their preoperative survey (“enriched population”), into a clinical trial where they received usual care or additional analgesic treatment (higher dose of spinal morphine combined with systemic acetaminophen and IV PCA).11 They found that this adjunct treatment significantly reduced acute pain scores at 24 hours, as well as pain on movement and average pain report.
6.5. Opioid receptor function/pharmacological challenge

Through sophisticated naloxone blockade studies, Bruehl et al. have found that endogenous opioid inhibition influences morphine efficacy. Specifically, in a randomized, counterbalanced, cross-over (3 single dose: morphine, naloxone, and placebo) study, they found that morphine efficacy is moderated by endogenous opioid function (evaluated through QST) in healthy participants and low-back pain patients. They confirmed this effect in a larger sample of chronic low-back pain patients, specifically finding that those with greater natural endogenous opioid inhibition experience less acute relief of back pain with morphine. A number of studies have evaluated how early response to a medication predicts long-term response, as well as infusion screening of IV lidocaine and ketamine in forecasting analgesic benefit (see Ref. 50 for review).

Proof-of-concept trials, given their exploratory nature, are uniquely suited to prespecify logical, mechanism-based treatment modifiers in the effort to advance personalized pain treatment, which can be assessed more thoroughly in larger, later-stage trials. Identifying biomarkers, potentially based on pathophysiological/psychobehavioral mechanisms, could inform study populations, appropriate subgroups, or new indications that will aid in customizing interventions and guide treatment choices. The logical next step would be the inclusion of systematic phenotyping routinely in trials to advance or refute such a symptom-/mechanism-based treatment approach.

6.6. Sex and gender

Over the past several decades, researchers have developed a deeper understanding of sex- and gender-related influences on clinical pain. A number of studies have provided evidence that pain processing may be different between men and women in response to both experimentally induced and clinical pain conditions. Various research and professional organizations have advocated for more research into the effects of sex and gender on pain, as well as for the inclusion of women in both preclinical and clinical research studies. Consequently, POC analgesic trials should consider study in both sexes.

Subgrouping patients by sex can shape numerous aspects in the design and interpretation of POC trials. Possible sex differences in response to experimental pain models may either limit the target patient population or broaden the overall generalizability of a study’s findings, thus guiding future studies. For example, one study of experimental endotoxemia as a model for inflammatory pain suggested that pain perception and modulation are more sensitive to immune activation in women than in men, whereas another group found no sex differences in endotoxin-induced pain sensitization. Researchers considering the use of such pain models must therefore carefully consider how sex may influence interpretation of findings. Another example of the potential value of studying experimental responses to pain in both sexes is the study of the placebo effect, which has important implications for clinical trial design based on expected response to placebo. Several studies have observed small, but significant differences in placebo effects and pain processing between men and women. Finally, an increasing number of studies are evaluating the effect of patient sex on clinical pain outcomes in response to a variety of analogics, from opioids to cannabis. Such studies can provide greater insights about which patients are most likely to benefit from which therapies, adding an important element to the development of personalized pain medicine.

7. Statistical issues

The nature of POC studies, with their small sample sizes and fewer endpoints, presents statistical challenges. Smaller sample sizes allow for easier recruitment, lower cost, and more efficient completion of a clinical trial, at the expense of diminished statistical power and potential inability to detect clinically significant effects. Therefore, POC studies typically need to deviate from the standard α (significance level or type I error probability) of 0.05 and β (type II error probability) of 0.1 (ie, 90% power) to remain cost-effective and may require more advanced statistical analysis techniques. In the IMMPACT recommendations on research designs for proof-of-concept chronic pain trials, an instructive example is given: consider 2 different chronic pain conditions, painful DPN vs pain HIV neuropathy. In a study of painful DPN, a higher type II error probability (false-negative) may be more acceptable because other efficacious treatments are available, whereas HIV neuropathy has very few efficacious treatments, and accepting a higher type I error probability (false-positive) would decrease the risk of missing a potentially beneficial therapy.

Because small sample sizes give individual subjects significant influence on study outcomes, appropriate participant selection is crucial to the success of a POC study. For POC trials evaluating preliminary treatment efficacy, appropriate inclusion and exclusion criteria must be formulated based on the POC to be studied, and these criteria must be rigorously applied to create appropriate homogeneity, thus maximizing statistical power and efficiency. By contrast, POC trials designed to identify target treatment populations may necessarily have a heterogeneous patient population, yet a small sample size would yield low power to detect a treatment effect in each subgroup. In such cases, an N-of-1 or cross-over study design may be more appropriate than the traditional parallel-group trial, although these may not always be feasible depending on the pain condition or treatment being studied.

Another important distinction between POC trials and confirmatory trials is the use of “early efficacy endpoints,” as opposed to clinical endpoints. For example, a POC pain study may assess a decrease in area of mechanical hyperalgesia as measured by QST for its primary endpoint rather than a decrease in pain score. The early endpoints used in POC trials theoretically have larger treatment effect sizes and can be assessed in shorter periods, allowing for smaller sample sizes to achieve adequate statistical power and faster evaluation of preliminary efficacy. However, appropriate early efficacy endpoints may not always exist, and even when they do, they may not correlate with meaningful clinical outcomes. Researchers should therefore carefully consider whether an early efficacy endpoint may be appropriate for their potential study, and furthermore, whether the increased potential for identifying analgesic efficacy will translate to significant clinical results in later trials.

Adaptive designs are another approach used in POC trials to reach meaningful conclusions in a shorter period than traditional clinical trials. As discussed previously, adaptive designs, such as adaptive dose-finding designs, adaptive allocation designs, group-sequential designs, and sample-size re-estimation designs allow for changes in study protocol and statistical analysis as new data are acquired. These changes may include adjusting randomization ratios or treatment allocation, modifying protocols, or changing sample size; such changes may increase the potential for bias or reduce the overall statistical power of the study. However, the ability to perform interim analyses and respond accordingly may be critical to the overall
success of the trial and may even help determine whether the trial should be continued. Therefore, adaptive designs require extensive planning and careful consideration of the many logistical and procedural challenges that may impede modifications to an ongoing study.\(^\text{10}^\) The precise nature and timing of all protocol changes and interim data analyses must be planned and described in the protocol before the initiation of the study to minimize potential errors in trial results, allow for clear interpretation of data, and provide valid conclusions.\(^\text{11}^\)

As with any study with a small sample size, conclusions drawn from a POC study may be difficult to generalize to a larger patient population. In addition, small studies are less likely to pick up rare but serious adverse effects that may only later be detected in much larger clinical trials. However, taking POC studies for what they are—limited, small-scale studies addressing a focused research area—provides a strong basis for future research and new opportunities.

8. Summary/future directions

Traditionally, POC clinical trials are studies where a drug (device or method; such as high-frequency spinal cord stimulation\(^\text{1}^\)) is examined for the first time for its biologic activity, efficacy, and safety in patients. For new molecular entities, POC trials are an essential component of the “exploratory development” phase that helps make the critical go/no-go decision—whether to embark on a larger, definitive clinical trial or to avoid wasting resources in a study that is likely to fail. The meaningful interpretation of POC trials of new drugs for pain requires evidence that the drug reaches the target (receptor occupancy), the drug affects the target (target engagement), and the drug affects pain signaling mechanisms in a dose-dependent manner.

Proof-of-concept trials have also been used as a research tool in the development and validation of new “pain models” and pain-related outcome measures, identification of physiological and pathological pain mechanisms, evaluation of biomarkers to predict chronic pain treatment outcomes, assessing the preliminary efficacy and safety of treatment strategies such as combination therapy, and others. Several preclinical and clinical models of chronic pain have been used to help determine the appropriate target patient population for POC trials and the presence of an “analgesic signal.” Both human experimental pain and clinical models have their strengths and limitations, and the appropriate model should be selected based on the understanding of the mechanism of action of the drug being tested.

The design of a successful POC trial requires careful consideration of the research objective, patient population, the particular intervention, and outcome(s) of interest. Proof-of-concept studies have used a variety of study designs in an attempt to enhance assay sensitivity and minimize the risk of a “false-negative” trial outcome. Although no one design may be uniformly applicable, enriched enrollment and adaptive designs may improve assay sensitivity and the efficiency of trials.

A challenge for future studies is adapting POC trials to address the emerging initiatives toward personalized/precision medicine. Personalization of pain management would require better insights on pain mechanisms in a given individual (phenotype), genetic factors (genotype), environmental, and behavioral factors influencing the pain experience. Although precision medicine is a worthwhile future goal, it adds a complexity to the design of appropriate studies that may require innovative large-scale research approaches.

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