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Improving study conduct and data quality in clinical trials of chronic pain treatments: IMMPACT recommendations

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Number of Pages 35
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Abstract

The estimated probability of progressing from phase 3 analgesic clinical trials to regulatory approval is approximately 57%, suggesting that a considerable number of treatments with phase 2 trial results deemed sufficiently successful to progress to phase 3 do not yield positive phase 3 results. Deficiencies in the quality of clinical trial conduct could account for some of this failure. An Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT) meeting was convened to identify potential areas for improvement in trial conduct in order to improve assay sensitivity (i.e., ability of trials to detect a true treatment effect). We present recommendations based on presentations and discussions at the meeting, literature reviews, and iterative revisions of this article. The recommendations relate to the following areas: (1) study design (i.e., to promote feasibility), (2) site selection and staff training, (3) participant selection and training, (4) treatment adherence, (5) data collection, and (8) data and study monitoring. Implementation of these recommendations may improve the quality of clinical trial data and thus the validity and assay sensitivity of clinical trials. Future research regarding the effects of these strategies will help identify the most efficient use of resources for conducting high quality clinical trials.

1. Introduction

The estimated probability of progressing from phase 3 analgesic clinical trials to regulatory approval is approximately 57%, suggesting that a considerable number of treatments with phase 2 trial results deemed sufficiently successful to progress to phase 3 do not yield positive phase 3 results. [31]. Potential explanations for this high rate of failure in late stage development include (1) false positive phase 2 trial results, (2) incorrect dosage selection based on phase 2 trial data, (3) phase 2 and 3 clinical trial design features that compromise assay sensitivity (i.e., the ability of a trial to detect a true treatment effect); for example, entry criteria that are too heterogeneous or inappropriate outcome measures, (4) insufficient increase in sample size between phase 2 and 3 to accommodate potential increased heterogeneity in the target population in larger, phase 3 trials, and (5) low quality execution of the phase 2 or phase 3 trial. Considering the burden on study participants, the risks of being exposed to new treatments, the possibility of receiving a placebo treatment, and the high costs of drug development [45], it is imperative that factors that impede the development of novel pain treatments with greater efficacy or safety be addressed. The Initiative on Methods, Measurement, Pain Assessment in Clinical Trials (IMMPACT), an interdisciplinary forum comprised of academic investigators, governmental representatives, industry scientists, and patient advocates, has previously provided recommendations for the design of phase 2 and 3 clinical trials with the aim of optimizing validity and assay sensitivity [18, 19, 28]. Improvements in clinical trial conduct can increase clinical trial validity, efficiency, and assay sensitivity and minimize participant burden. The purpose of this article is to describe considerations for proper execution of clinical trials to ensure that efforts made at the design stage to improve validity and assay sensitivity in analgesic clinical trials are not impeded by poor study conduct.

2. Methods

An IMMPACT consensus meeting was held that was comprised of an international group of participants from universities, government agencies, industry, and patient advocacy

organizations. Participants were selected on the basis of their research, clinical, or administrative expertise relevant to the execution of clinical trials. The meeting was designed to reflect a broad representation of relevant disciplines and perspectives while limiting the size to promote productive and efficient discussion. The recommendations described in this article are specifically applicable to pharmacologic trials, although most of them also apply to clinical trials of other interventions, including devices and psychological and physical interventions.

To facilitate discussion, background lectures were presented at the meeting. These lectures and the meeting transcript are at the following website: http://www.immpact.org/meetings/Immpact18/participants18.html. The considerations discussed in this article are based on the background presentations, meeting discussion, and iterative revisions of manuscript drafts. A scoping review that aimed to identify peer-reviewed publications related to clinical trial quality in the study of pain treatments was also performed to provide an evidence base for the recommendations included in this article. The search terms and results are presented in Appendix 1. A narrative review of the general medical literature as well as articles cited in the background presentations at the meeting or identified in the co-authors' reference libraries were reviewed and searched for relevant references, which were then retrieved, reviewed, and incorporated in this article when appropriate. The draft manuscript was revised in an iterative process of circulation and revision by all authors until consensus was achieved; the final version of the article was approved by all authors. Many of the recommendations in the article are evidence based, from recent research on randomized clinical trials of treatments for chronic pain and a substantial number of meta-analyses of methodologic aspects of clinical trials of major depression and other psychiatric disorders.

3. Recommendations

3.1. Study design

The first step to ensure data quality involves the development of a study protocol that is feasible for the sites involved in the trial. Pain trials have terminated early due to lack of

feasibility, for example, participants not wanting to discontinue extensive list of excluded medications (Harrison). When designing eligibility criteria, investigators should consider consulting with study sites and therapeutic area experts regarding the feasibility of recruiting a sufficient number of appropriate and representative participants. Although a homogenous study population generally provides greater assay sensitivity [19], if recruitment is very challenging, site investigators may intentionally or unintentionally include participants who do not precisely meet eligibility criteria [34, 40], or seek eligibility exceptions for potential participants who are close to the eligibility cut-off values. It would be better for investigators to identify which entry criteria could be revised considering any trade-off between the recruitment benefit and a potential loss in assay sensitivity.

The number and complexity of study measures and assays can have an impact on study feasibility. Although it may be tempting to include multiple measures and assays for exploratory analyses, it is important to consider the burden that these measures will place on the participants and study staff. Undue assessment burden will decrease the motivation of study staff to recruit patients to the study, especially in the context of other, simpler studies competing for potential participants at a site that might provide relatively greater compensation [21]. Too many assessments may also decrease individuals' willingness to enroll or continue in the trial. Although we are unaware of research that investigates the number and duration of PROs that would be likely to cause participants to carelessly complete the forms, future research on this topic using strategies similar to those employed by the survey research field (Curran, 2016) would be valuable to inform clinical trial design. Additionally, if participants are asked to complete too many patient-reported outcome measures, they may not think carefully about each questionnaire item, potentially compromising the quality of the data for outcome measures that address the primary aim of the trial. Finally, complicated study protocols increase the likelihood of participant non-compliance, protocol deviations or violations, and missing data. Overall,

investigators should consider the balance between the optimal (from a scientific perspective) study design and what is feasible to conduct a trial yielding high quality data [27].

3.2. Site selection and staff training

Large phase 3 trials require a large number of sites. According to clinical trials.gov, recent industry-sponsored trials in osteoarthritis, chronic low back pain, diabetic peripheral neuropathy, and post-traumatic neuropathic pain included between 35 and 153 sites. The number of participants recruited per activated trial site ranged from 3.5 to 10.7. Investigators should aim to include sites with a track record of producing high quality data for studies that utilize procedures similar to the current trial. For early phase trials and smaller studies, similar site evaluations should be conducted to the extent possible and relevant. Sites with highly experienced clinical investigators and staff and requisite resources are most desirable. The population-wide prevalence of the target pain condition should be considered to determine the approximate number of sites required to complete the trial in a timely manner. For example, less common or more complex conditions may require more sites and sites that have particular expertise and resources. Based on the experience of the authors a site visit by sponsors of multi-site clinical trials to confirm the experience of potential study sites to conduct the study is typically worthwhile. It is also prudent to determine whether any regulatory agencies or similar bodies have cited the investigator and whether issues related to any such citations have been resolved. Similar considerations apply when planning for multi-site trials regardless of the funding source and for establishing government-sponsored research site networks.

Investigators should be cautious about implementing strategies to accelerate recruitment (e.g., increasing financial incentives to site staff or participants when recruitment is slower than expected) or adding less experienced sites. Some evidence suggests that participants enrolled at sites added toward the end of large multisite trials may demonstrate a smaller treatment effect than those enrolled earlier [37], possibly due to laxity of recruitment practices or reduced compliance with protocol standards.

A relatively recent approach to improving study conduct is training site staff to avoid heightening participant expectations, with the goal of minimizing the placebo effect. Such training could potentially improve the assay sensitivity of clinical trials by (1) decreasing a "floor effect" (i.e., reduced ability to detect a significant group difference because the placebo group has improved so much that the active group cannot do much better [19]), and (2) reducing improvements in pain in the placebo group without reducing improvements in pain in the active group [62]. Note that the possibility of such selective effects on the placebo group assume a "sub-additive" mechanism in which the observed effect in the treatment group is lower than the sum of the non-drug specific placebo effects and the treatment-specific effects [36]. Training to manage participant expectations could include providing guidance on neutral introduction of the experimental treatment to minimize the effects of the study introduction on participant expectation bias (e.g., explaining the uncertainty regarding the efficacy of the treatment rather than emphasizing that a novel drug may be efficacious). In support of neutral presentation strategies, staff training in combination with study materials designed to introduce the treatment in a neutral way has been shown to decrease the response to a placebo but not an active treatment for asthma [62].

3.3. Participant selection

Many factors contribute to decisions regarding appropriate eligibility criteria in a clinical trial. Given the objectives of this article, we emphasize issues related to participant selection that can affect the quality of the data including (1) participants' ability to accurately report their pain, (2) blinding of study staff to certain eligibility criteria (e.g., minimum pain severity) to prevent unintentional or intentional encouragement of symptom inflation, and (3) efforts to reduce the number of "fraudulent" participants who attempt to enroll in clinical trials as a means of financial gain.

Study participants' abilities to accurately and consistently report their pain intensities vary. A retrospective analysis of data from multiple clinical trials of peripheral neuropathic pain

conditions demonstrated that greater variability of pain intensity ratings in the baseline week

was associated with lower effect sizes [24]. Similar results were obtained in an analysis of a

single trial of fibromyalgia patients [30]. High variability in baseline pain ratings could also reflect

major fluctuations in pain intensity experienced by participants, especially for certain conditions

in which pain is intermittent (e.g., trigeminal neuralgia). However, excessive variability in pain

intensity ratings during the baseline week for a particular participant could be due, at least in

part, to decreased ability to conscientiously report pain. A recent study of osteoarthritis pain

[53], showed a significant correlation between the degree of variability in baseline pain ratings

and the accuracy of pain ratings as measured by a test that evaluates the consistency of pain

ratings in response to various intensities of experimental pain stimuli. This cross-over study also

showed that higher consistency of rating experimental pain was associated with a larger

response to naproxen (vs. placebo). Given the available data linking decreased assay sensitivity

to high variability in baseline pain ratings [24, 30] and ability to consistently rate pain in

response to experimental pain stimuli [53], excluding participants based on such criteria should

be considered when designing chronic pain trials in order to improve assay sensitivity [19].

Unfortunately, no evidence-based consensus exists for the definition of "high" or "excessive"

variability (e.g., standard deviation) in baseline pain ratings that should be used to exclude

participants to increase assay sensitivity. The potential increase in assay sensitivity should be

balanced against the challenge of further shrinking the pool of eligible participants. Similarly, if

participants rate their "least pain" greater than their "average pain" or "average" pain greater

than "worst pain", they either do not understand or are not paying sufficient attention to the

items assessing these domains. Such participants could therefore be excluded from

randomization. An alternative to excluding these participants may be to train participants to be

more careful when reporting their pain (see Section *3.4. Participant training*)*.*

When there is undue influence to recruit participants (e.g., abnormally high financial

incentives for site staff or pressure to complete enrollment), investigators and study staff may

unintentionally or intentionally reveal key eligibility criteria to potential participants. For example, if the protocol excludes participants with highly variable baseline ratings, study staff could mention to potential participants that highly variable ratings are undesirable. A similar phenomenon has occurred in antidepressant trials where the baseline ratings on the Hamilton Depression Rating Scale from the clinician-investigators who were aware of the entry criteria tended to be: (1) higher than participant self-reported ratings and (2) frequently met the minimum for inclusion when the participant-reported ratings did not meet this minimum for inclusion [34, 40]. Blinding investigators and study staff to as many eligibility criteria as possible and implementing a centralized process to decide on participant eligibility may help eliminate such effects on participant selection [19]. Centralized eligibility review may also decrease the number of protocol violations related to inappropriate enrollment.

A recently recognized threat to data quality is the inclusion of "fraudulent" participants, that is, potential participants who report a pain condition that they do not actually have, embellish or fabricate symptoms of their actual diagnosis, or hide comorbidities that would lead to exclusion from trials [6, 17]. Such participants often attempt to join multiple trials at once or even enroll in the same trial at different sites [46]. A study by Shiovitz et al. [47], determined that 3.5% of participants who were screened at 9 sites throughout Southern California for central nervous system-related trials were identified as being almost certainly duplicate participants (i.e., the same individual attempting to join the same trial at 2 different sites in the registry).

Devine and colleagues [16] proposed multiple strategies to combat enrollment of fraudulent participants including (1) confirming participant-reported diagnoses in clinical records or with treating physicians whenever possible, (2) designing telephone scripts that conceal the reason for exclusion by either completing the entire script regardless of the point at which the potential participant becomes ineligible, or using dummy questions after the actual reason for exclusion has occurred, (3) minimizing or masking the key entry criteria that are published in registries like clinicaltrials.gov, (4) minimizing the emphasis of payments in advertising (e.g.,

mentioning compensation, but not revealing the total amount) (5) training staff to recognize professional participants' focused attention on reimbursement rather than study risk and/or benefit, and (6) utilizing research registries. Various clinical trial registries have been developed recently to identify potential duplicate participants, including CTSdatabase [1], DUPCHECK [2] and Verified Clinical Trials [3]. These registries use various measures and variables to identify duplicate participants within and among clinical trials. As part of the trial consent process, participants consent to entering their information in a database at the time of screening and to allow the investigator to receive information from the registry regarding the participant's previous and current enrollments. The registry can then make a determination whether the potential participant should be excluded from the current study based on their history of enrollment in the same and other clinical trials. Some of these registries have the capacity to alert investigators if the potential participant has enrolled in another clinical trial too recently, has reported exclusionary diagnoses based on criteria from previous trial enrollment, or has already enrolled in the current trial at another clinical site. These technologies can also be used *post hoc* in order to identify potentially duplicate participants who enrolled in the same trial at multiple sites for use in sensitivity analyses.

3.4. Participant training

Several training strategies have been developed to improve the accuracy of participants' reported pain ratings. Note that pain rating training should be performed prior to randomization to ensure that all ratings contributing to the data analyses have been implemented after training. One type of training requires participants to rate their pain in response to various intensities of painful pressure stimuli. The results in the form of pain ratings vs. intensity of stimuli plots are presented to the participants. Any "outlier" pain ratings are highlighted to inform the participant of high variability in their ratings. Participants typically undergo 2 – 4 rounds of training before being randomized in a clinical trial. A recent study demonstrated that this type of training decreased the response to placebo treatment compared to no training of participants [54].

However, the study did not specifically demonstrate that the participant training affected the placebo group response more than the active group response, which would be necessary for a training to improve assay sensitivity. Future studies aimed at evaluating the effect of training on the magnitude of the effect of treatment (vs. placebo) are necessary to rigorously evaluate the utility of this approach for increasing assay sensitivity [29].

A second type of pain intensity rating training uses a multifaceted approach to improve the accuracy of participants' pain intensity ratings. The approach includes instructing participants to (1) sit in a quiet and comfortable location to focus on their pain, (2) focus only on the type and site of pain that is being studied, and (3) create personalized anchors for the anchors on a pain scale, which generally describe 10 as the "worst pain imaginable" (example personal anchors: 1 = slight soreness and 10 = leg amputation without anesthesia) to be used consistently throughout the duration of the study. In a longitudinal study, this training was shown to increase the percentage of participants who rated least pain < average pain < worst pain as one would expect for accurate pain ratings [50]. Implementation of this method in clinical trials may improve accuracy of pain intensity ratings and thereby increase assay sensitivity; however, a 4-arm trial with active and treatment arms that do and do not incorporate training is necessary to confirm that the training is associated with a statistically significant increase in the standardized effect size [29].

Training participants to more accurately rate their pain and excluding individuals based on apparent inconsistent pain rating both have advantages and limitations. Excluding potential participants will make recruitment more challenging. This strategy could also be criticized for decreasing generalizability, although it is not clear that individuals who may pay less attention to accurately reporting their pain would respond differently to treatment than individuals who more accurately report their pain. Pain rating training will increase the costs associated with executing the trial to varying degrees depending on the complexity and time demands of the program.

Participant training may also include attempts to minimize the so-called "therapeutic misconception" (i.e., the belief by some participants that the goal of the trial is to provide them with the best possible healthcare without fully understanding that the trial is actually an experiment to evaluate the efficacy of a treatment that may not be beneficial). If participants have this type of misconception, expectation bias and thus the placebo response may be increased, leading to smaller treatment effect sizes because of "floor effects" [19]. Education to minimize the therapeutic misconception and clear communication that accurate pain intensity ratings are more useful than improved pain intensity ratings are both important to promote high quality, accurate data.

3.5. Treatment adherence

The efficacy as well as the safety profile of a therapy can only be determined if participants in a trial adhere to the treatment as it is prescribed. Non-adherence has been found to be a confounding factor in the results of multiple clinical trials, decreasing the observed efficacy of truly efficacious treatments and also causing temporary bouts of toxicity that would not occur with proper adherence [4, 9, 25, 38, 39]. Non-adherence to pharmacologic treatments can be due to purposeful action or forgetfulness. If participants experience adverse events (AEs) from the treatment, they may purposefully not adhere to the treatment regimen in an attempt to minimize those AEs. This can lead to discontinuation or alteration of dosing early in the trial. Forgetfulness can lead to intermittent skipping of doses or taking doses too closely together. When doses are skipped, drug levels can decrease below the target concentration (i.e., the minimum effective concentration), thereby sacrificing efficacy; when doses are taken too closely together, drug concentrations may surge and AEs could occur more frequently [8]. Multiple factors have been identified to be associated with medication non-adherence (i.e., non-initiation, suboptimal implementation, early discontinuation), which makes non-adherence difficult to predict [32].

Strategies to educate participants about the importance of adherence should systematically be performed at initiation of treatment and during follow-up. For example, if AEs are likely to be temporary, educating participants on their transient nature could prevent participants from altering dosing or discontinuing therapy early in the study. Although education is an enabling strategy that may enhance participant adherence, it does not alone ensure adequate treatment adherence over the course of the study. Monitoring adherence during a study and providing participants with periodic feedback has been shown to be the most effective strategy to improve medication adherence [61]. In addition to promoting adherence, data from adherence monitoring systems can be used to explain potential efficacy failures and unexpected AEs in clinical trials and help direct decisions regarding future research [25, 43].

Different methods to measure treatment adherence provide different levels of accuracy regarding patterns of treatment adherence. Maximizing the accuracy and granularity of the data should be balanced with costs and participant burden. For example, counting the number of pills remaining at each study visit (i.e., "pill count") is inexpensive and confers no additional burden on the participants; however, at best, this practice only provides information regarding the overall number of pills self-dispensed in a study period rather than temporal patterns of medication-taking behavior. Additionally, participants can easily discard pills prior to arriving at a study visit. For example, one study of HIV prophylaxis showed that while pill counts suggested 86% compliance, only 30% of biospecimens contained detectable drug levels [39].

Electronic detection of package opening using monitored caps or blister packs creates a detailed dosing history and does not add participant burden, except potentially for participants having difficulty with dexterity or cognitive impairment. This method does not prove drug ingestion, but research combining such electronic monitoring with pharmacokinetic data has shown 97% concordance between package opening and ingestion [60]. An ingestible sensor can be added to pills to track when participants ingest medication, avoiding potential pitfalls of participants removing pills but not taking them. However, this method is intrusive for the

participants as it requires that they wear and maintain a patch, it requires drug reformulation, and it only applies to solid oral formulations. Participants can also be asked to monitor their usage in electronic diaries or by videotaping themselves taking the medication using mobile technology. These methods might add participant burden and complicate the dosing routine, which could have an inadvertent negative effect on treatment adherence. The advantages and limitations of these methods are discussed in more detail in a recent review [60]. The authors concluded that using electronic detection of package opening is a low complexity/high impact strategy to improve drug development. Accurate dosing history information has the potential to result in more informative safety data and to better inform dosing regimens for future trials or clinical use.

Measuring and maximizing treatment adherence involves different considerations for non-pharmacologic interventions such as cognitive behavioral therapy, physical therapy, and massage. Such trials should include monitoring of fidelity to the intervention in at least random samples of participants. Such monitoring could include investigator observation either in person or in recorded therapy sessions (e.g., [11]).

The negative effects of poor treatment adherence discussed in this section are now recognized by more and more stakeholders, prompting initiatives to improve adherence and its reporting, as well as utilization of adherence data to inform clinical trial interpretation [14, 23, 58]. For example, a trial of pregabalin for HIV neuropathy by Simpson et al. [48] monitored medication adherence using self-report and pharmacokinetic data. The trial did not detect a significant treatment effect of pregabalin in the primary intention-to-treat analysis. The investigators also reported a sensitivity analysis including only participants who appeared to have reasonable medication adherence and still did not detect a treatment effect, suggesting that lack of adherence was not likely the reason that the trial yielded a non-significant result.

3.6. Data collection

The practice of using electronic Clinical Outcome Assessment (eCOA) in place of paper case-report forms (CRFs) and paper participant-reported outcome (PRO) measures likely increases data quality by removing errors introduced at the data entry stage of the clinical trial [21]. Based on our authors experience, most chronic pain clinical trials are now using eCOA for pain ratings. When completed at home on a computer or smartphone, eCOA may decrease response bias to "please the investigator" since the participant is not completing the outcome questionnaires in front of study personnel. Utilization of electronic reminders such as text messages could improve response rates for PRO measures that are completed outside the research center [49]. Electronic versions of PROs that have been validated in the paper format should mimic the original instrument as much as possible. For example, questions that are on the same paper page should be kept on the same screen, and if the anchors for 1, 3, and 5 on a Likert scale are illustrated for each question on the paper copy, they should be on the electronic copy as well. In cases where the PRO must be modified significantly to be implemented electronically, studies to demonstrate the construct validity of the electronic version compared to the original may be necessary (e.g., [12]). The U.S. Food and Drug Administration (FDA) has published a guidance on best practices for documenting electronically captured data [57], including the necessity to comply with 21 CFR part 11 in order to protect participant privacy.

Improved methods to optimize the assessment of reasons for withdrawal from clinical trials need to be developed and evaluated. Currently, single reasons for withdrawal are often cited when participants drop out from pain trials when in fact motivation for withdrawal is likely multifaceted (e.g., the participant is only experiencing minor benefit along with AEs, or the trial visits are burdensome given the relatively modest pain relief that the participant perceives). Not only are single reasons for withdrawal typically captured, the reason is often poorly described, such as "participant withdrew consent." A method to assess reasons for withdrawal that elicits all or most contributions to a participant's decision to drop out of a trial as well as the relative importance of each reason would be highly informative when describing the benefits vs. the

drawbacks of a therapy. Such information also has the potential to improve future trial design if trial burden is a factor in withdrawal for a high percentage of participants. Additionally, a better understanding of reasons for withdrawal would be valuable for developing statistical models that accommodate missing data. For example, this information can inform post-withdrawal assumptions concerning the conditional distribution of outcomes in pattern mixture models that use control-based imputation [13]. In these models, one can make different assumptions about how participants would have responded had they remained in the trial, given their observed outcomes. For example, for those who dropped out for reasons related to the treatment (e.g., lack of efficacy or AEs), one might assume that their outcomes after dropout would be like those in similar placebo-treated participants who remained in the trial. For those who dropped out for other reasons (e.g., burdensome visit schedule or moved from the area), one might assume that their outcomes after dropout would be like those in similar participants in their treatment group who remained in the trial.

3.7. Data and study monitoring

FDA and other regulatory agencies require that investigators and study sponsors ensure "proper monitoring of the investigations" and that "the investigation(s) is conducted in accordance with the general investigational plan and protocols" (21 CFR 312.50). Even though it is not explicitly required, industry sponsors have historically used 100% source data verification (SDV), which is costly, time-intensive, and prone to human error, to satisfy this requirement [35, 45, 51]. A study of trials conducted between 2004 and 2012 found that data monitoring contributed to approximately 14% of phase 3 clinical trial costs [45]. Furthermore, an analysis comparing 100% SDV to partial SDV found marginal benefit from 100% SDV [5]. These data, and others [55], suggest that 100% SDV may not be cost effective and that it is prone to human error, leaving room for improvement by using more recent risk-based monitoring systems.

Both the FDA and European Medicines Agency (EMA) have published guidance encouraging consideration of risk-based monitoring approaches in clinical trials [22, 56]. Risk-based monitoring requires a monitoring plan that focuses efforts on those aspects of the clinical trial that are most important (e.g., entry criteria, informed consent, and primary outcome measures) or most challenging (e.g., testing that is not part of standard clinical practice, adherence monitoring). It could also, for example, focus monitoring efforts on relatively inexperienced sites. Random SDV, declining SDV, tiered SDV, and mixed SDV approaches are types of risk-based approaches that modify the percentage of SDV depending on the quality of data identified by the early SDV efforts or the relative importance of the data [42].

Risk-based approaches can also utilize centralized statistical monitoring to identify potentially problematic sites or data points for further investigation in place of some or all regularly scheduled on-site SDV. These approaches use pre-specified rules with automated flags to alert investigators or sponsors to abnormalities in the data. Examples of abnormalities that could be flagged include missing data, data outliers, and protocol deviations. Comparisons among sites with respect to enrollment rates, variation in outcome measures, or ranges of outcome measures can be used to identify "abnormal" sites that may require greater in-person monitoring, or site retraining [15, 20]. In addition to identifying lower performing sites, these programs have been used to detect fraud within sites [26, 33, 41, 44, 52]. Importantly, when the abnormal data alerts are automated, they are not as susceptible to human error.

Retrospective analyses have demonstrated that centralized monitoring could identify many of the errors that were identified using on-site SDV. [7]. [10].

In addition to the specific resources needed to support risk-based monitoring, it is necessary to have a pre-specified monitoring plan that outlines the rules that will be used to flag data quality issues (e.g., > 5% missing data for the primary outcome variable), the actions that will be taken in response to any issues that are identified, and how amelioration of the issues will be monitored. It is also important to emphasize that although centralized monitoring is a

valuable option for monitoring data, certain aspects of the trial cannot be monitored centrally. For example, in-person visits are required to ensure the proper storage of the investigational drug and to identify potential under-reporting of AEs that may not be suggested by differences among sites in the frequencies of AEs [42].

Important challenges exist with centralized monitoring. It is difficult to identify outliers in small samples, and the amount of data at each site is likely to be low early in trial recruitment and can remain low throughout the trial for a substantial portion of sites, particularly in trials for rare conditions. Interim statistical monitoring typically occurs using a version of the database that has not undergone complete error resolution; therefore, the results can be subject to data entry errors. Some variation between participants recruited at different sites is common due to regional or cultural differences; for example, variability in screen failure rates due to co-morbid conditions may be different in different countries. Thus, a central monitoring plan must account for these differences when identifying site outliers [59].

4. Conclusion

In attempting to maximize the validity and assay sensitivity of clinical trials, high quality study execution and sound clinical trial design are both important. Possible explanations for the high rate of failed phase 2 and 3 chronic pain trials include deficiencies in trial execution as well as inadequacies in study design (e.g., insufficient statistical power). Table 1 summarizes recommendations for improving trial conduct and data quality. Future research regarding the impact of implementing these strategies will help identify the most efficient use of resources to conduct high quality clinical trials.

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Table 1. Considerations for improving quality of clinical trial conduct and data

Trial conduct domains	Considerations	Level of evidence
Study design	(1) Consider feasibility when developing the protocol through consultation with study sites and content area experts.	(1) D, E
Site selection and staff training	(1) Select sites based on: • Previous experience of CRO or sponsors • Expertise regarding unique populations or study procedures • Publically available lists that could identify low-performing sites (2) Consider implementing staff training aimed at decreasing participant expectations	(1) E (2) D [62]
Participant selection	(1) Consider excluding participants with highly variable baseline pain intensity ratings or inappropriate ordering of "worst" "average" and "least" pain ratings (2) Employ strategies to minimize enrollment of fraudulent participants	(1) B [24], C [30, 53] (2) D [6, 16, 17, 46, 47]
Participant training	(1) Train participants to improve accuracy of pain intensity ratings using one of the methods outlined in the text.	(1) C [54], E
Treatment adherence	(1) Promote treatment adherence with education and monitoring-based feedback. (2) Consider reliable and precise methods to measure patient adherence in clinical trials, including intermittent blood sampling and electronic monitoring. (3) Consider performing sensitivity analyses to assess the effects of treatment adherence on efficacy and safety outcomes.	(1) D [61], E (2) D [60], E (3) C [48], E
Data collection	(1) Consider using electronic clinical outcome assessments to minimize data mistakes due to transcribing errors. (2) Record complete reasons for withdrawal (including potentially multi-factorial reasoning) while avoiding undescriptive terms like "withdrew consent" or "investigator decision" whenever possible.	(1) E, F [57] (2) D [13], E
Data / study monitoring	(1) Consider alternatives to 100% source data verification to enhance data quality, including risk-based monitoring programs based on centralized statistical monitoring.	(1) D [5, 7, 10, 15, 20, 45, 55, 42, E, F [56]

Levels of evidence: A. Meta-analysis or systematic review, B. Retrospective quantitative analysis of multiple RCTs, C. Qualitative analysis of RCTs or research studies in pain, D. Qualitative analysis of RCTs or research studies in conditions other than pain, E. Expert experience / consensus. F. FDA recommendation

Appendix 1.

The search terms in the below table were utilized in PubMed in conjunction with (AND clinical trial AND pain):

*Note a separate search was run specifically for articles mentioning "quality of life" and these hits were removed from the quality search above due to the result of ~1800 hits).

The search was conducted on 6-18-2018

Term	Number of hits	Number of full text articles screened	Number of relevant articles cited in the paper
Clinical Trial			
Quality	1810 (495 without "quality of life" articles)		
Integrity	35	1	0
Patient training	0	0	0
Compliance	154	1	0
Monitoring	156	1	0
Fabrication	3	0	0
Deception	1	0	0
Misbehavior	0	0	0
Adherence	146	4	0
Site selection	1	0	0
Site training	0	0	0
Site surveillance	0	0	0
Statistical monitoring	0	0	0
Statistical quality	0	0	0
Data quality	3	1	0
Fabricate	49	0	0