OptiMeth | CRPS

OPTIMISING CLINICAL TRIAL METHODS FOR
COMPLEX REGIONAL PAIN SYNDROME

A Methodological Framework for Optimising Clinical Trial Methods for **Complex Regional Pain Syndrome (CRPS)**

Authors: The OptiMeth-CRPS Network Group

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KMS was the project lead and is the guarantor, he conceived and designed the project, was awarded the funding and drafted the white paper. All named authors attended meetings, provided project-related content and edited the white paper. All authors have reviewed and approved the white paper.

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Contents

Summary

Complex regional pain syndrome (CRPS) is a rare and disabling pain disorder. Systematic reviews have identified a critical lack of adequately powered, high quality clinical trial evidence to inform the management of CRPS. There is an urgent need to find solutions to the methodological challenges of undertaking clinical trials in CRPS. The aim of the 'Optimising clinical trial methods for complex regional pain syndrome' (OptiMeth-CRPS) network project was to develop a methodological framework for optimising the planning, design, conduct and reporting of future clinical trials in CRPS (OptiMeth-CRPS).

We employed an 'Experience and expertise' approach to develop a methodological framework. The framework was developed by an international group with expertise in the lived experience of CRPS, CRPS research, clinical trials, CRPS evidence synthesis and rare disease research methods. We used an iterative process of i) online and face-to-face meetings, ii) reviewing and approving meeting notes detailing the group's discussions and iii) revising draft manuscripts to develop the framework.

This white paper presents the discussions and recommendations of the OptiMeth-CRPS network project. The OptiMeth-CRPS methodological framework presents nine key optimisation strategies for improving the planning, design, conduct and reporting of CRPS trials. These include strategies for optimising i) the trial team, ii) research questions, iii) trial governance and management, iv) trial design, v) the trial population, vi) intervention and comparator groups, vii) trial outcomes, viii) data analysis, and xi) openness, transparency and reporting.

The OptiMeth-CRPS methodological framework is offered as a tool to support the CRPS research community to undertake high quality clinical trial research and improve the quality of the evidence upon which clinical decisions and guidelines for the management of CRPS are based.

Plain Language Summary

Complex Regional Pain Syndrome (CRPS) is a rare pain disorder associated with significant disability. There's a critical lack of high-quality research on treatments for CRPS. This project aimed to create a guide to improve the way future clinical trials on CRPS are conducted.

An international team of experts, including people living with CRPS and researchers, worked together to develop this guide. They used a step-by-step process involving online and in-person meetings, reviewing discussion notes, and revising draft manuscripts to create the final guide.

The 'OptiMeth-CRPS Framework' outlines nine steps for improving CRPS trials:

1. Forming a capable trial team that involves patients and the public
2. Creating clear research questions
3. Managing trials well
4. Designing rigorous trials
5. Choosing suitable trial participants
6. Choosing and comparing treatments appropriately
7. Measuring outcomes that are meaningful to people living with CRPS
8. Evaluate the findings correctly
9. Making sure everything is clearly and fully reported

This framework is offered as a tool to support the CRPS research community to perform high quality clinical trials when testing different treatments for CRPS.

1

Background

Complex regional pain syndrome (CRPS) is a rare, complex, painful and disabling condition that can occur after acute trauma, surgery or spontaneously.[47] Diagnosis is based on a cluster of characteristic symptoms and signs, known as the 'Budapest criteria'.[75]

Current understanding of the pathophysiology of CRPS implicates multiple complex mechanisms linked to inflammation and autoimmunity, vasomotor dysfunction, central nervous system alterations, genetic susceptibility, and psychological distress.[47] Population estimates suggest an incidence of somewhere between five and 26 cases per 100,000 person-years,[120] as such CRPS is a rare condition.[47] Living and coping with CRPS is challenging. It can have a far-ranging adverse impact on health-related quality of life and the physical and social disability associated with living with CRPS persists in the long term for some sufferers.[97,98, 116,132] Emerging evidence suggests a genetic predisposition in combination with an environmental trigger may contribute to the development of CRPS.[17,152]

Guidelines for the treatment of CRPS recommend an interdisciplinary multimodal approach, comprising rehabilitative, psychological, educational, pharmacological and interventional pain management strategies.[74,65] However, determining the optimal approach to therapy remains uncertain despite the availability of numerous clinical trials.[48]

Cochrane overviews[48] and systematic reviews[126,131,158] have identified a critical lack of high-quality evidence underlying most interventions for CRPS. This is due to the rarity of CRPS and the associated challenges of recruiting and retaining sufficient numbers of participants but also to inadequacies in basic aspects of trial planning, design, conduct and dissemination. Clinical trials involving people with CRPS are often characterised by sampling limitations (small sample sizes, single-centre recruitment), diverse outcome measures and short-term follow-up periods. Furthermore, they often lack pre-registration, have no published protocol and are incompletely reported.[74,158] Improperly planned, designed, conducted and reported clinical trials contributes to the waste of valuable research (i.e. economic, human, material) resources.[93]

In the absence of high-quality evidence supporting CRPS interventions, making treatment decisions and recommendations is extremely challenging for clinicians, clinical guideline developers and people living with CRPS. Consequently, there is an urgent need to find solutions to the methodological and practical challenges of undertaking clinical trials in a rare chronic pain condition such as CRPS. Potential solutions could arise from optimising scientific quality and rigor throughout the clinical trial lifecycle, from ideation to dissemination,[119] including planning, designing, conducting, reporting processes as well as considerations of internal and external validity.[99] Additional solutions could come from optimising methodological, statistical and operational trial efficiency.[178] An efficient trial is one that answers the research question robustly and accurately using the fewest resources. Achieving efficiencies in clinical trials in general and rare conditions such as CRPS specifically are highly desirable given the limited availability of human, economic and material resources.

There are currently no CRPS-specific methodological frameworks aimed at improving the scientific quality of clinical trials of interventions for CRPS. A methodological framework that optimises trial methods may enable CRPS trialists to better fill the evidence void and in doing so, enhance the quality of the evidence upon which clinical guidelines and care are based.

1.1 Project aim

The primary aim of this project was to create a methodological framework that optimises the scientific quality of future clinical trials investigating the effects of interventions for people living with CRPS. For the purpose of this project, 'scientific quality' refers to optimal practice in the planning, design, implementation and dissemination of clinical trials.[99]

2 Methods of methodological framework development

2.1 Study registration

This project was registered on the Open Science Framework (OSF) (https://doi.org/10.17605/OSF.IO/894MQ) eight days after the first meeting. Ethical approval was not required for this project.

2.2 Project design

We employed an 'Experience and expertise' approach to develop a methodological framework.[122] A methodological framework 'provides structured practical guidance or a tool to guide the user through a process'.[122] An experience and expertise approach utilises the collective knowledge and experience of a group of experts to identify the issues and topics to inform and shape the framework and then iteratively develop the framework by synthesising and amalgamating the documented discussions of the group.[122]

2.3 Setting

The project was coordinated from University College Dublin, Ireland by the project lead (KS). Three online (using a video conferencing platform) and two 2-day meetings (hosted in University College Dublin) were held between July 2023 to May 2024.

2.4 Participants

The methodological framework group comprised 14 purposefully sampled individuals based on their knowledge and expertise in i) the lived experience of CRPS and/or patient advocacy (VAF, EC), ii) CRPS clinical trials (FB, SB, MCF, CM, NEO), iii) orthopaedic clinical trial methods and management (DJK), iv) CRPS clinical guidelines (FB, SB, SG, CM), v) CRPS core outcome set development (FB, SB, SG, CM), vi) CRPS-related evidence synthesis (KS, MCF, NEO) or vii) rare disease methodology and biostatistics (SD, R-DH, FK, SN). One project assistant (CI) compiled meeting notes.

Of the 15 members, six were based in the United Kingdom (CM, SG, VAF, SD, DJK, NEO), three in Ireland (KS, CI, EC), two in Germany (FB, RD-H) and one each in Australia (MF), Austria (FK), Greece (SN), and the United States of America (SB).

2.5 Procedure

Five meetings, chaired by the project lead, were scheduled to provide sufficient time and opportunity for the group to propose and discuss methodological issues and generate intellectual content for the framework. We used an iterative process of i) online and face-to-face meetings, ii) reviewing and approving meeting notes detailing the group's discussions and iii) draft manuscript revisions to develop the framework. Group discussions focused on optimising trial methods for CRPS as a rare multidimensional pain condition.

2.6 Deviations from protocol

Use of the Nominal Group Technique was not required to develop the final framework, which was achieved instead through group discussions, reviewing and approving meeting notes and revising draft manuscripts.

3

The OptiMeth-CRPS Methodological Framework

As we considered the nature of the limitations underlying the design, conduct and reporting of many existing trials of interventions for CRPS[38,126,131,158] we identified opportunities for optimising a range of generic (e.g. following reporting standards), contemporary (e.g. enhancing Equality, Diversity and Inclusiveness) and rare disease (e.g. trial designs) aspects of CRPS trials in addition to those specific to CRPS itself.

The OptiMeth-CRPS Methodological Framework presents nine key optimisation strategies for improving methodological rigor within and across the planning, design, conduct and reporting of phases of CRPS trials. These include strategies for optimising:

1. The trial team
2. The research question
3. Trial governance and management
4. Trial design
5. The trial population
6. The interventions and comparator groups
7. Trial outcomes and follow-up
8. Data analyses
9. Openness, transparency and reporting

A summary of the framework is presented in Figure 1 and as 'cheat sheets' (Appendix 1). A summary of our recommendations is presented in Table 1. We acknowledge the significant overlap and interrelatedness between trial components and phases. Also, our discussions made reference to numerous published guidelines, frameworks and recommendations (summarised in Table 2). Meeting notes detailing the discussions at each meeting are available online (**https://doi.org/10.17605/OSF.IO/894MQ**.

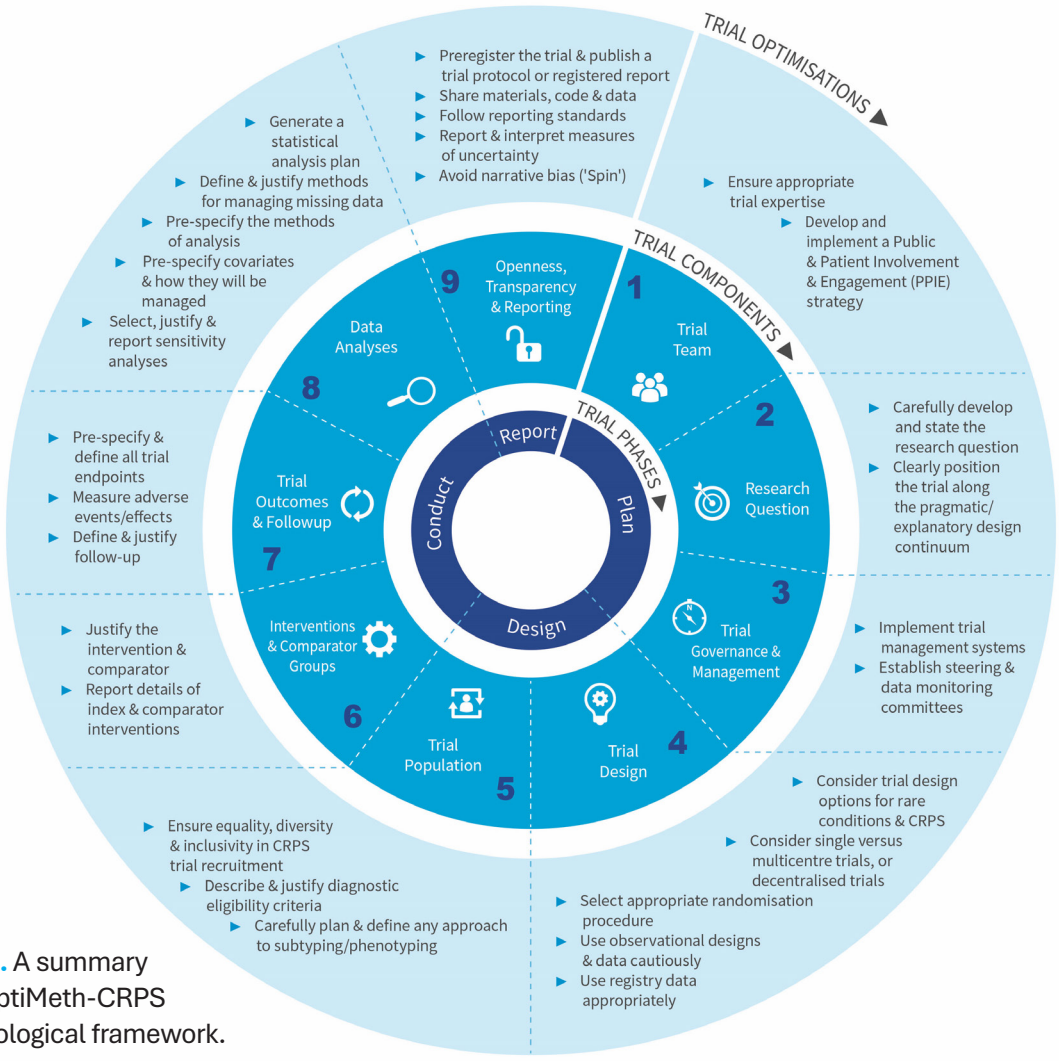

Figure 1. A summary of the OptiMeth-CRPS methodological framework.

Table 1. Summary of OptiMeth-CRPS trial components and recommendations

Component	Recommendations
Optimising the trial team	• Assemble a team with sufficient expertise to deliver a safe and robust trial • Include people with lived experience of CRPS and CRPS-advocacy groups to facilitate research meaningful to those living with CRPS
Optimising the research question	• Formulate the research question carefully and clearly in order to focus the trial's purpose
Optimising trial governance and management	• Proactively manage the financial, legal, ethical, administrative, quality assurance and control aspects
Optimising trial design	• Select a trial design appropriate to the research question, and in light of the expertise and resources available
Optimising the trial population	• Implement enrolment strategies that promote equality, diversity and inclusivity for participants • Clearly define and justify trial eligibility criteria, aligned to the research question and aims and objectives of the trial
Optimising the intervention and comparator groups	• Select, justify and evaluate interventions appropriate to their stage along the development-evaluation lifecycle • Report the nature and parameters (e.g. dosage) of all interventions (including control/placebo) according to the TIDieR guideline [87]
Optimising trial outcomes and follow-up	• Prespecify, justify and report all trial outcomes (primary, secondary, exploratory, adverse event) at all time points in full and in accordance with the CONSORT Outcomes 2022 Extension[20]
Optimising data analysis	• Generate a statistical analysis plan prior to undertaking analyses detailing the analytical approach, statistical methods, any preplanned sensitivity analyses and strategies for managing missing data and covariates
Optimising openness, transparency and reporting	• Preregister and prospectively publish a trial protocol or registered report in accordance with the SPIRIT guideline[23] • Make trial materials and data Findable, Accessible, Interoperable and Reusable (FAIR)[176] • Follow reporting guidelines appropriate to the trial's design and methods (see 'Enhancing the Quality and Transparency of Health Research' (EQUATOR) Network) • Report all deviations from protocol and post hoc decisions • Avoid spin bias

Table 2. Resources for optimising CRPS trials

Topic	Resources	
Optimising the trial team	Assessing trial team competency	• Global Health Training Centre: **Global Competency Framework for Clinical Research**
	Public and patient involvement and engagement (PPIE)	• The Initiative on Methods, Measurement, and Pain Assessment (IMMPACT): Patient engagement in designing, conducting, and disseminating clinical pain research: IMMPACT recommended considerations[78] • 'Guidance for Reporting Involvement of Patients and the Public' (GRIPP2): GRIPP2 reporting checklists: tools to improve reporting of patient and public involvement in research[159]
Optimising the research question	• PICO (Population, Intervention, Comparison, and Outcomes)[144] • The Estimands Framework: a primer on the ICH E9(R1) addendum[101] • Pragmatic Explanatory Continuum Indicator Summary (PRECIS-2) tool[114]	
Optimising trial management	• UK Trial Managers' Network: **The Guide to Efficient Trial Management** • National Institute for Health and Care Research (NIHR): **The Clinical Trials Toolkit**	
Optimising trial design	Designs for rare conditions and smaller populations	• International Rare Diseases Research Consortium (IRDiRC) Small Population Clinical Trials Task Force[32] • Integrated designs and analysis of small population clinical trials (IDeAl) project[84]
	Decentralised trials	• European Medicines Agency 2022: **Recommendation Paper on Decentralised Elements in Clinical Trials** • National Institute for Health and Care Research: **Remote Methods of Trial Delivery**
	Pragmatic trials	• Research objectives and general considerations for pragmatic clinical trials of pain treatments: IMMPACT statement[88] • Methods for pragmatic randomized clinical trials of pain therapies: IMMPACT statement[89]
	Pilot and feasibility trials	• Pilot and feasibility studies: extending the conceptual framework[14]
	Randomisation procedure	• ERDO - a framework to select an appropriate randomization procedure for clinical trials[86]
	Causal interpretations from observational studies	• Causal inference about the effects of interventions from observational studies in medical journals[29]
	Evaluating the quality of observational and registry data	• Registries for Evaluating Patient Outcomes: A User's Guide[2] • Towards a core set of indicators for data quality of registries[77] • A systematic review: Tools for assessing methodological quality of human observational studies[173]

Table 2. Resources for optimising CRPS trials (cont.)

Topic	Resources	
Optimising the trial population	Equality, diversity and inclusivity	• Making Pain Research More Inclusive: Why and How[95] • FOR EQUITY: **Health Inequalities Assessment Tool** • National Institute for Health and Care Research (NIHR): **NIHR INCLUDE** • International Association for the Study of Pain (IASP): **Global Inequities in Pain Treatment: How Future Research Can Address This Better** • Journal of Pain. Confronting Racism in Pain Research. Three paper series available from: **www.sciencedirect.com/journal/the-journal-of-pain/vol/23/issue/6** • Sex and Gender Equity in Research: rationale for the SAGER guidelines and recommended use[80] • Challenges with embedding an integrated sex and gender perspective into pain research: Recommendations and opportunities[107]
	Accessible and understandable participant information leaflets/informed consent forms	• Preparing accessible and understandable clinical research participant information leaflets and consent forms: a set of guidelines from an expert consensus conference[27]
	CRPS subtyping/ phenotyping	• Patient phenotyping in clinical trials of chronic pain treatments: IMMPACT recommendations[39]
Optimising intervention and comparator groups	Developing, planning and evaluating interventions	• Medical Research Council guidance for developing and evaluating complex interventions[156] • Feasibility, Reach-out, Acceptability, Maintenance, Efficacy, Implementation, Tailorability (FRAME-IT)[68] • Reach, Efficacy, Adoption, Implementation, and Maintenance (RE-AIM)[62]
	Comparator and control groups	• Recommendations for the development, implementation, and reporting of control interventions in efficacy and mechanistic trials of physical, psychological, and self-management therapies: the CoPPS Statement[90] • The Selection of Comparators for Randomized Controlled Trials of Health-Related Behavioral Interventions: Recommendations of an NIH Expert Panel[54] • European Network for Health Technology Assessment (EUnetHTA): **Comparators and Comparisons. Criteria for the choice of the most appropriate comparator(s). Summary of current policies and best practice recommendations**
Optimising trial outcomes and follow-up	General	• Guidelines for Reporting Outcomes in Trial Reports. The CONSORT-Outcomes 2022 Extension[20]
	CRPS	• Core Outcome Measurement Set For Complex Regional Pain Syndrome Clinical Studies (COMPACT)[70]

Table 2. Resources for optimising CRPS trials (cont.)

Topic	Resources	
Optimising data analysis	Statistical analysis plans	• Guidelines for the content of statistical analysis plans in clinical trials[56] • Early phase clinical trials extension to guidelines for the content of statistical analysis plans[91]
Optimising openness, transparency and reporting	Trial protocols	• SPIRIT 2013 explanation and elaboration: guidance for protocols of clinical trials[23]
	Trial reporting guidelines	• Enhancing the QUAlity and Transparency Of health Research (**Equator Network**) • Checklist for the preparation and review of pain clinical trial publications: a pain-specific supplement to CONSORT[59]
	Reporting uncertainty	• Communicating scientific uncertainty[50]

3.1 Optimising the trial team

3.1.1 Expertise

We advise CRPS trialists to carefully reflect on the clinical, scientific, methodological and lived experience expertise required for their trial and to assemble a clinical trial team with the necessary education, training and experience to deliver a safe and robust trial.[45] Trial teams can assess their competency to run trials using the 'TDR Global Competency Framework for Clinical Research'.[64] We specifically recommend that CRPS trialists include a suitably qualified biostatistician on the trial team and consult with them from ideation to completion of the trial since their expertise is vital when planning, designing, conducting, analysing and reporting clinical trials.[139] This recommendation applies to multiple facets of the OptiMeth-CRPS framework described hereafter; we reiterate it selectively.

3.1.2 Public and Patient Involvement and Engagement (PPIE)

We recommend that CRPS trialists develop and implement a PPIE strategy for including people with lived experience of CRPS and CRPS-advocacy groups within trial teams, to facilitate research meaningful to those living with CRPS. People living with CRPS, and their representatives can valuably contribute their expertise and experiences to CRPS trial design (e.g. specifying the research question), conduct (e.g. advising on recruitment and retention) and dissemination (e.g. co-writing plain language summaries),[6] and their involvement should be meaningful and not tokenistic.[94] The Initiative on Methods, Measurement, and Pain Assessment (IMMPACT) recommendations for enhancing engagement with patient and advocacy partners in pain research provides guidance for enhancing PPIE across all stages of a trial's lifespan.[78]

CRPS trialists should consider the specific challenges of pain and mobility faced by PPIE contributors living with CRPS when deciding the nature, place and timings of engagement. We encourage CRPS trialists to agree early with their PPIE partners, and remain flexible, on the scope of involvement, include them on trial steering/management committees and ensure their inclusion and participation is adequately resourced in funding applications and trial plans. PPIE has been successfully implemented in CRPS-related research to co-create an infographic to help support people living with CRPS,[10] develop a core outcome set [70] and inform trial design and conduct.[67] 'Guidance for Reporting Involvement of Patients and the Public' (GRIPP2)[159] is also available.

3.2 Optimising the research question

3.2.1 Developing the research question

The research question critically informs subsequent trial design and methodological decisions.[28] Poorly focused or underdeveloped research questions may compromise the internal and external validity of a clinical trial.[46] Therefore, CRPS trialists should carefully and clearly formulate their research question (and subsequent hypotheses, aims and objectives) *a priori*, in order to focus the trial's purpose, make clear distinctions between exploratory (hypothesis generating) and confirmatory (hypothesis testing) trials and express the hypothesised relationships between the variables under investigation.[46] For CRPS trials this could include specifying the aim of the trial (e.g. demonstrating superiority or non-inferiority), clinical

characteristics of the CRPS population of interest (e.g. acute or chronic presentations, upper or lower limb) and the primary outcome of interest (e.g. pain intensity or quality of life).

CRPS trialists should use the 'Population, Intervention, Comparison, and Outcomes' (PICO) approach to help frame and focus their research question according to the population of interest, intervention to be tested, type of control or comparator against which the intervention is to be compared, and the outcome(s) used to measure the effect of the intervention.[144] Trialists might also consider using an estimands framework (i.e. a structured description of the treatment effects their trial aims to quantify) as an extension of the PICO approach to help clarify their research question.[40,101]

3.2.2 Positioning the trial along the explanatory – pragmatic design continuum

In stating the research question, we encourage CRPS trialists to consider where their trial is located along the explanatory/efficacy (could an intervention work in ideal circumstances) – pragmatic/effectiveness (does an intervention work in everyday clinical practice) trial continuum. CRPS trialists should clearly state *a priori* whether the purpose of their trial is to investigate the efficacy of an intervention in an explanatory trial, or effectiveness in a pragmatic trial. Positioning a trial along the explanatory – pragmatic continuum will help inform how a trial's hypotheses, aims and objectives, and conclusions are presented and have important implications for the design and relative internal and external validity of clinical trials.[57] The Pragmatic Explanatory Continuum Indicator Summary (PRECIS-2) tool[114] and other guidance[57] is available to assist CRPS trialists in their determinations. We acknowledge that such judgements are not always binary, and trials may have both explanatory and pragmatic objectives.[63]

The IMMPACT group has recently provided methodological guidance for trialists planning pragmatic trials of treatments for people experiencing pain specifically.[88,89] We advise CRPS trialists to carefully consider and follow this guidance which invites trialists to consider their choice of trial design, bias minimisation strategies and trial methods.

3.3 Optimising trial governance and management

Good governance and management can optimise the quality, operational efficiency and safety of clinical trials (World Health Organisation 2024). Trial governance and oversight can be provided by trial steering and data monitoring committees. Operationally, trial management systems can be implemented to augment and monitor trial planning, conduct and quality,[117] often at the direction of a trial manager.[105] Guides to aid CRPS trialists manage the financial, legal, ethical, administrative, quality assurance and control aspects of their clinical trials are available.[129,166] Proactive trial management helps ensure the viability of the trial and the integrity of its findings.[154]

3.4 Optimising trial design

3.4.1 Trial designs for rare conditions and smaller populations

Different trial designs provide distinct opportunities to achieve efficiencies; for example, by optimising enrolment (e.g. decentralised trials; N-of-1 designs) or requiring fewer participants for the same level of statistical power (e.g. crossover designs); by allowing trialists to test two or more interventions in a single trial (e.g. factorial designs) or shortening the duration of the trial (e.g. adaptive designs). Decisions about trial design ultimately stem from the research question and invariably involve trade-offs between the advantages and disadvantages of a given trial design and between the desired efficiencies and the resources available.[178]

Algorithms to assist selecting between trial designs specifically involving people with rare conditions and smaller populations have been described.[26,71] These algorithms involve the selection of trial designs based on a range of disease-, recruitment-, outcome- and intervention-related characteristics. We make no specific recommendations concerning trial design because the decision will be likely based on a multitude of factors (e.g. available expertise, financial resources, research setting, regulatory environment etc.) and are best determined by individual trial teams. We considered the advantages and disadvantages of the different trial designs within these algorithms and their applicability to CRPS trials (summarised in Table 3).

Table 3. Advantages and disadvantages of different trial designs for Complex Regional Pain Syndrome as a rare condition (adapted from[26,71])

Trial design	Main features	Advantages	Disadvantages	Applicability to CRPS trials
Parallel	Participants are randomised to one of two (or more) treatment groups	Comparatively simple to design and conduct Well understood and accepted	Larger sample sizes can be required compared to other designs Typically last longer and more costly to run than many other designs	Highly applicable. Probably provide the simplest, most robust estimate of between-group differences in outcomes
Factorial[102]	Participants are randomised to one of four treatment groups (2x2 factorial trial), i.e. i) treatment A alone; ii) treatment B alone; iii) both treatments A and B; or iv) neither A nor B	Enables the evaluation of more than one intervention in the same trial Can be very efficient regarding required resources and sample size (e.g. 2x2 trial is equivalent to two parallel trials requiring around twice the sample size)	More complex design; can be challenging to implement Requires and assumes the effects of the different active treatments are independent (i.e. no interaction between the treatments). Where an interaction is expected and is of interest it can be estimated using this trial design but inflates sample size requirements resulting in some loss of efficiency	May be applicable if independence of treatment effects can be adequately justified or accounted for in the design.
Crossover	Participants receive both index and control interventions according to a randomly assigned treatment sequence	Guaranteed exposure to the index intervention may improve enrolment Participants act as their own control, balancing covariates and reducing variability Require smaller sample sizes	More suitable for trials involving chronic, stable conditions and interventions with quick onset and short-lasting effects Assumes participants' health status is comparable at the start of each treatment period. Adequate washout period required before crossover to remove potential carryover effects from the initial intervention Typically last longer which may increase attrition rates	May be applicable only if symptomatic and clinical stability of the CRPS sample can be reasonably expected; hypothesised treatment effects are short-lived and/or adequacy of the washout period can be assumed

Table 3. Advantages and disadvantages of different trial designs for Complex Regional Pain Syndrome as a rare condition (adapted from[26,71]) (cont.)

Trial design	Main features	Advantages	Disadvantages	Applicability to CRPS trials
N-of-1[79,153]	A single participant receives periods of treatment according to a randomized sequence of multiple crossovers between treatment and comparison groups (e.g. A-B-A-B; where one period "A" is the index treatment and the other period "B" is a comparison treatment (e.g. control, or no intervention)	Optimising treatment for an individual patient Guaranteed exposure to the index intervention may improve enrolment Participants act as their own control, balancing covariates and reducing variance (Individual) N-of-1 trials for several patients using the same protocol offer the opportunity to pool study results	Same as for crossover design Less useful for providing generalisable estimates of treatment effectiveness but meta-analysis of individual N-of-1 trials might be useful for estimating population effects (homogenous outcome measures required)	Same as for crossover design Might be useful for rare conditions such as CRPS, participants otherwise excluded from trials, (e.g. children, people with comorbidities or on concurrent treatments), investigating subgroups responses to treatment
Randomised withdrawal	All participants initially receive the index treatment; non-responders are withdrawn; responders are then randomised to continue treatment or receive placebo/ control	Useful for investigating optimal duration of treatment (in patients who respond to the treatment) May increase statistical power for a given sample size	Treatment effects may be overestimated as only responders proceed to randomisation Limited generalisability as the study population is treatment responders only	Might be useful for people with chronic, stable CRPS symptoms; investigating subtypes of CRPS People with CRPS may be unwilling to be randomised to a placebo/control after experiencing benefit
Adaptive[36]	A family of trial designs allowing pre-planned changes to an ongoing trial's design or statistical procedures in response to accumulating trial data without compromising the validity of conclusions	Can achieve efficiency by reducing the required sample size (e.g., by dropping interventions or stopping early through meeting pre-specified utility or futility margins prior to reaching the full target sample size)	Highly complex to design, implement and analyse Can be more resource intensive in the design and conduct phases Some designs may risk rejecting potentially efficacious/effective treatments Planning and budgeting challenging as final sample size can often be uncertain	Could be applicable to drug trials. Applicability to multimodal and non-drug trials unknown

A separate framework proposed a series of operational, methodological and statistical modifications to conventional parallel designs in order to increase the feasibility of recruitment or reduce the sample size required.[136] Our group recognised the utility of some initial parts of that framework (increasing the enrolment and/or follow-up times; collaborating nationally and internationally) but believed subsequent steps (e.g. relaxing power and/or the alpha level by a small amount) would elevate the risk of a type I error (false positives) and lessen the precision of effect estimates.

Additional generic recommendations for the design and analysis of trials for rare conditions have been described by the International Rare Diseases Research Consortium (IRDiRC) Small Population Clinical Trials Task Force[32] and the 'Integrated designs and analysis of small population clinical trials' (IDeAl) project[84] and other research consortia.[85,109,124] These recommendations address patient engagement, trial design, methods and data analysis which may be useful to CRPS trialists when planning their trials.

We recommend that CRPS trialists explain and justify their choice of trial design, ensure its consistency with the research question, and acknowledge any associated assumptions and limitations underlying their choice within their trial protocol.

3.4.2 Trial designs for CRPS

Systematic reviews of interventions for CRPS have demonstrated use of both parallel and crossover trial designs.[84,131,158] Our group considers that most situations will call for conventional parallel trial designs. Crossover trials (where participants receive both index and control interventions according to a randomly assigned treatment sequence), and N-of-1 trials (singular or in series) as a variant of multiple crossover trials[153] are a viable and efficient option where symptomatic stability can be reasonably expected and where the intervention is hypothesised to deliver only short term benefits. Washout periods to negate carryover effects (when the effect of the first treatment alters the effect of the next treatment) prolong participation and follow-up which may increase participant dropout rates.[26] Such losses are important because each participant in a crossover trial acts as their own comparator, resulting in twice the information loss compared to a participant in a parallel trial.[71] We advise caution in the use of crossover designs in people with CRPS. Variability of CRPS symptoms and signs[108,149] may result in period effects (when the effect of the same treatment received at two different periods is different for each period) and carryover effects (when a previous treatment influences the effects of a subsequent treatment).[112]

Factorial trial designs (where two or more interventions are assessed in a single study) can increase efficiency by allowing evaluations of more than one intervention in a single trial without increasing the required sample size, although this efficiency depends on the assumption of no interaction (i.e. synergistic or antagonistic effects) between compared treatments.[102] The assumption of independence is not plausible in all contexts, and if violated, estimates may be biased. Potential interactions can be accounted for in the trial design but this inflates sample size requirements resulting in some loss of efficiency. We know of one registered ongoing CRPS trial employing a factorial design.[7]

Randomised withdrawal designs involve all participants receiving the index treatment initially after which 'non-responders' are withdrawn, and responders are randomised to continue treatment or receive a placebo/control intervention.[26] The limitations of this design are similar to those for crossover trials. They may also overestimate treatment effects as only responders proceed to randomisation, also limiting the generalisability of findings.

Adaptive trials designs (e.g. Sequential Multiple Assignment Randomized Trials, multi-arm multi-stage) are a newer family of designs that allow pre-planned changes to an ongoing trial in response to accumulating trial data without compromising the validity of conclusions.[36] Adaptation options are potentially numerous but can include revising the sample size requirements in response to inaccurate assumptions of study design parameters, stopping a trial arm early in response to sufficient evidence of efficacy, futility or safety concerns or changing the treatment allocation ratio to favour treatments indicating beneficial effects.[36] We are not aware of any previous or ongoing CRPS trials employing adaptive designs. Adaptive designs can be combined with other trial designs and each other.[71] We strongly recommend CRPS trialists consult with an experienced trial biostatistician if considering using a more logistically and methodologically complicated adaptive design to confirm suitability and viability.

With appropriate biostatistical support, CRPS trialists could also use computer-based simulation methods during trial planning to compare different trial designs[11], investigate their sensitivity to various sources of bias[86] and optimize the design.[55] These simulations may usefully inform discussions about the design choice with stakeholders.

3.4.3 Single versus multicentre trials

Decisions concerning the use of single versus multicentre clinical trials are likely based on a range of financial, logistical, operational and methodological factors. Single centre trials are likely to be logistically simpler to conduct, less resource intensive and maybe appropriate for testing new interventions before undertaking more expansive and expensive trials.[72] However their findings are less generalisable and are associated with slightly larger estimates of treatment effects compared to multicentre trials.[167] Potential causes of this phenomenon include i) higher risk of bias (methodological and publication), ii) the selection of a more homogeneous participants, and iii) greater standardisation of interventions and measurement.[8]

Multicentre trials may be preferable in order to help achieve sample size requirements, particularly for a rare condition such as CRPS, reduce risk of bias and enhance the generalisability of findings.[151] The International Research Consortium for Complex Regional Pain Syndrome (**https://www.crpsconsortium.org/**) provides a forum to facilitate research collaborations and multicentre clinical trials involving people living with CRPS. However, multicentre trials are invariably more challenging to conduct, coordinate and manage, more resource intensive, and require careful protocol adherence, quality assurance and data management processes.[24,30] Also, multicentre trials usually involve centre-stratified randomization and stratified analyses. Heterogeneity of the treatment effects between centres may influence overall trial findings and need to be investigated.[123] In some cases, where the number of patients per centre is small, stratification by centre cannot be implemented and study results must be interpretated relying on the assumption of no heterogeneity of treatment effects between centres.

3.4.4 Decentralised trials

The aforementioned factorial CRPS trial[7] also employs a decentralised trial design. In decentralised trials aspects of recruitment, enrolment, informed consent, delivery of study interventions and data collection may be conducted at locations other than clinical trial sites, through telemedicine, mobile/local healthcare providers or digital technologies.[5,170] By enabling broader equity of access and reducing participant burden, especially for people living with a painful and disabling condition such as CRPS for whom hospital visits can be extremely challenging and expensive, decentralised trials may improve participant enrolment, engagement and retention and by extension the quality of trial data and the accuracy of findings.

However, decentralised trials are associated with various safety, privacy and scientific validity challenges.[170] For example, since there are currently no validated self-report CRPS diagnostic screening measures, fully decentralised trials using telemedicine may necessitate modifications to how diagnostic eligibility criteria are applied (e.g. trial participants submitting photographs or videos of their limb or involving a partner to help with temperature and sensory tests to support a CRPS diagnosis). Decentralised trials may also influence which outcomes can be measured or interventions tested. For example, use of outcome measures (e.g. CRPS severity score[76] or serology for biomarkers) or interventions (e.g. pharmacological agents or devices) that require in-person medical administration or supervision may not be suitable.

Guidelines are available to assist in planning and conducting decentralised trials.[41,130]

3.4.5 Randomisation procedure

We recommend that CRPS trialists select a randomisation procedure (e.g. simple, block, stratified) appropriate to the research question and characteristics of the trial. In trials for rare conditions different randomisation procedures have distinct advantages and disadvantages.[110] For example, simple randomisation may lead to imbalances in sample size and baseline characteristics (i.e. covariates) between treatment and control groups[4] which may reduce the precision of effect estimates. The 'Evaluation of Randomization procedures for Design Optimization' (ERDO) framework may assist trial teams to select the randomisation procedure which best mitigates the impact of selection bias (associated with the selection of patients who may have a higher probability of responding to treatment) and chronological bias (associated with changes in population characteristics, diagnostic ability, or learning effects arising from prolonged recruitment periods for rare conditions) on the study result.[86]

3.4.6 Observational designs and data

Whilst the use of data from non-randomised or observational studies to evaluate the effects of interventions was considered, our group recognises the potential biases and likelihood of confounding are larger in studies employing these designs compared with randomized trials.[143] Findings from observational studies should always be interpreted with caution and at best be considered exploratory and hypothesis generating rather than confirmatory. We acknowledge that others may hold different views concerning the merits of drawing causal inferences about the effects of interventions from observational studies.

Given that causal interpretations of effect estimates from observational data are based on specific and often unverifiable assumptions[96] we invite CRPS trialists employing non-randomised or observational designs to evaluate the effects of interventions for CRPS to be clear about the limitations imposed by such designs when interpreting their data and drawing conclusions. A recently proposed framework to help researchers identify if and when causal interpretations from observational studies might be appropriate could be useful to CRPS trialists considering such designs.[29]

3.4.7 Registry data

Registry-based randomised controlled trials (rRCTs) are pragmatic trials that use existing patient data from registries to facilitate various clinical trial procedures such as recruitment and collection of outcome data.[155] A planned international clinical research registry for CRPS may provide data useful to CRPS trialists in the future.[69] Depending on the type and quality of data available, observational and/or trial data from rare disease patient registries can be useful to trialists when planning a clinical trial. For example, registry data may be useful for estimating parameters to inform sample size estimates and appropriate and meaningful endpoints.[51] Registry data could also be helpful in generating hypotheses about subgroups which can then be tested in a prospective RCT.

It is possible to use observational/natural history data to supplement or replace a control arm in a clinical trial[175], although this requires careful consideration and planning and is often based on a range of conditions (e.g. data quality) and assumptions (e.g. that predicted treatment effects are large in comparison to the effect of potential biases).[61] We are not aware of the use of observational/registry data in CRPS trials although guidance for the use of natural history data during drug development is available[51] and a pain-specific implantable device registry might be useful to some CRPS trialists.[142]

We recommend CRPS trialists use guidance and frameworks for evaluating the quality of observational and registry data when appropriate.[2,77,173]

3.5 Optimising the trial population

3.5.1 Equality, diversity and inclusivity in CRPS trial recruitment

In response to evidence of systemic inequalities in pain research (including racism, sexism, ageism, classism and ableism), attention has been given to promoting equality, diversity and inclusivity (EDI) in pain research, science and practice and enhancing stakeholder representation.[95,134] Our group supports and acknowledges the need for CRPS trialists to purposefully design in and implement equal, diverse and inclusive recruitment strategies for trials involving people living with CRPS in order to increase the representation of under-served (e.g. non-native language speakers), minoritised (ethnic minorities) and marginalised (e.g. people from lower socioeconomic strata) groups. Doing so helps ensure trial samples better reflect the communities intended to benefit from the trials' findings, optimising their representativeness and generalisability.[31]

One way to address the challenges of recruiting sufficient numbers of people with CRPS into trials is to ensure that no one living with CRPS is excluded from participation due to language, logistical or cultural barriers.[13] We acknowledge the challenges of implementing principles of EDI and that CRPS trialists will have to think creatively about engaging under-served communities.

We encourage CRPS trialists to implement recommended strategies for improving inclusiveness in pain research, such as: i) forming a diverse trial team, ii) facilitating cultural competency training for trial staff, iii) undertaking stakeholder/community engagement, iv) adopting inclusive recruitment and data collection practices, and v) budgeting for EDI strategies.[52,95] Resources exist to assist CRPS trialists optimise trial inclusiveness and accessibility and address potential inequalities in pain research (see Table 2). For CRPS trialists, and the pain trial community more broadly, the 'Inclusion, Diversity, Equity, Antiracism, and Accessibility' (IDEAA) reporting guideline is available to help promote and report a trial's equity strategy and findings in accordance with current best practice.[135]

CRPS trialists can further enhance trial EDI by collecting inclusive and equity-relevant demographic data that enables the analysis and reporting of disaggregated trial outcome data based on sociodemographic variables (e.g. sex, gender, ethnicity, socioeconomic status).[106] This will make clear the generalisability of findings and facilitate future exploratory (meta-)analyses to identify potential demographic differences in treatment effects.[106, 134] General[80] and pain research-specific[107]

recommendations are available to assist CRPS trialists address sex and gender differences when designing, conducting and reporting their trials.

3.5.2 CRPS diagnosis for eligibility

The Budapest criteria for CRPS[75] are the international standard for CRPS diagnosis and should be used to standardise trial eligibility and comparability, although our group noted that reliability can be challenging in multicentre and/or international trials.[30] We discourage the use of outdated diagnostic labels (e.g. reflex sympathetic dystrophy, causalgia, post-stroke shoulder-hand syndrome) and criteria (e.g. 'Veldman' criteria).[48,158]

However, given the rarity of the condition trialists might consider using modified CRPS diagnostic criteria, i.e. 'CRPS with Remission of Some Features' for people who previously but no longer meet the Budapest criteria but who have some but not all ongoing symptoms and signs.[66] Relaxing eligibility criteria allows CRPS trialists to expand the potential population from which participants might be recruited and increases the likelihood of reaching sample size requirements, but caution is required as doing so may increase sample heterogeneity and reduce comparability with trials using standard Budapest criteria. Decisions regarding the selection of diagnostic eligibility criteria could depend on where the research question is located on the pragmatic/explanatory continuum, where explanatory (efficacy) trials typically require the use of more stringent diagnostic criteria to enhance internal validity whereas pragmatic (effectiveness) trials may use less stringent clinical criteria based on 'real-life' clinical populations, to enhance external validity.[58]

Our group acknowledged the tension that exists in deciding between eligibility criteria for a rare condition such as CRPS that, if too narrow, may exclude too many patients or if too broad may introduce heterogeneity into the study sample. Ultimately, trialists should clearly describe and justify their eligibility criteria in order to optimise replicability, and to allow the applicability and generalisability of findings to be appraised. The need for trialists to thoroughly describe the clinical characteristics of their CRPS sample (e.g. affected limb, limb dominance, participation in work/studying, inciting event, diagnostic symptoms and signs present, location and duration of symptoms) has been highlighted[61,70], since they are sometimes incompletely reported.[158]

Our group noted a potential ethnic bias in the clinician-determined CRPS diagnostic criteria (skin colour changes/asymmetry) given that the Budapest criteria do not account for differences in skin colour. Validation of CRPS diagnostic criteria in people with different skin colours should improve their inclusivity, reliability and applicability.

3.5.3 CRPS subtyping/phenotyping

Distinct subtypes (or phenotypes) of CRPS have been explored and described (e.g. acute/chronic; warm/cold; dystonic/non-dystonic) based on hypothesised variations in the pathophysiological mechanisms underlying its presentation.[108] Different mechanistic subtypes of CRPS may potentially benefit from treatments known or hypothesised to target those mechanisms, in an attempt to optimise treatment outcomes.[118,133] For example, a warm (i.e. more inflammatory) mechanistic subtype may require and respond better to anti-inflammatory-based interventions compared to a cold (i.e. less inflammatory) subtype.[18,37] However, evidence for the validity of subtypes of CRPS is not yet sufficient to justify their use in confirmatory (hypothesis testing) clinical trials.[108]

The IMMPACT group has provided specific recommendations for patient subtyping/phenotyping in clinical trials of chronic pain treatments based on a number of possible domains, including: psychosocial factors, symptom characteristics, sleep patterns, responses to noxious stimulation, endogenous pain-modulatory processes, and response to pharmacologic challenges.[39] The extent to which CRPS might reflect subtypes according to these domains is not currently known. We therefore encourage CRPS trialists with an interest in phenotyping and subgrouping to further investigate the validity of these subtyping domains using appropriately designed studies.[104] For example, CRPS trialists might define subtypes and then analyse them as potential effect modifiers.[49]

Methodologically, CRPS trialists can follow general recommendations if planning to conduct 'subgroup' (synonymous with subtype but without an implied shared mechanism) analyses, [15,19,42,49,73,104] including:

- Defining and justifying subgroups *a priori* (pre-randomisation) on the basis of their relevance to the research question and including them within the statistical analysis plan. Any post-randomisation subgroup analyses should be clearly labelled as such.
- Confirmatory subgroup analyses should be based on formal tests of interaction (i.e. statistical tests to determine if there is an interaction between the treatment effect and the variables that define subgroups) and not by comparing the effect of treatment on the outcome separately within each subgroup (i.e. separate subgroup-specific analyses of treatment effect).

- Trials should be adequately powered to accommodate subgroup analyses and ascertain the absence/presence of subgroup effects. It is likely that any subgroup analyses within CRPS trials will be underpowered and should be framed as exploratory and hypothesis generating.
- When trialists include subgroup analyses, emphasis should almost always remain on the overall treatment effect rather than subgroup effects.
- Subgroup analyses can be unreliable (false positives secondary to multiple comparisons, false negatives secondary to inadequate power) and should be interpreted with caution.
- Subgroup effects should be validated sequentially though hypothesis-generating, hypothesis-testing and replication (external validation) studies before changing clinical practice.

3.6 Optimising the intervention and comparator groups

3.6.1 Justifying the intervention and comparator

A recent overview of systematic reviews of interventions for treating pain and disability in adults with CRPS found that many included trials tested interventions against active comparators without prior evidence of efficacy using placebo control[48], suggesting that trialists may be moving to comparative effectiveness trials prematurely.

When planning future trials, we encourage CRPS trialists to systematically evaluate existing data on efficacy and effectiveness in order to justify the selection of their intervention(s), frame their research question, inform intervention parameters (i.e. components, dosage, mode of delivery etc.) and avoid unnecessary replication and research waste. If such data are absent, CRPS trialists should undertake exploratory proof of concept/hypothesis generating studies in accordance with the intervention development and evaluation lifecycle.[68,156] Such preliminary, intervention development studies are required to support the biological plausibility, feasibility, tolerability, acceptability, adherence, fidelity, safety, and potential scalability of prospective interventions before undertaking more complex and costly clinical trials[9,138,140,150,160,179]

Frameworks to assist CRPS trialists with planning and evaluating early- and mid- to late-stage health interventions, such as 'Feasibility, Reach-out, Acceptability, Maintenance, Efficacy, Implementation, Tailorability' (FRAME-IT)[68], Reach, Efficacy, Adoption, Implementation, and Maintenance (RE-AIM)[62] and the Medical Research Council's guidance for developing complex interventions[156] are available. An additional framework presents specific design considerations for CRPS trialists undertaking pilot (internal and external) and feasibility studies.[14]

Our patient insight partners highlighted the need for CRPS trialists to provide quality plain language information within participant information resources that more clearly distinguishes between trials investigating established (e.g. pragmatic trials) in contrast to more novel or experimental (e.g. mechanistic, exploratory trials) interventions.

CRPS trialists must also make choices regarding the type of intervention against which the index intervention is compared, including a placebo intervention (placebo controlled trial), an inactive/attention control, another active intervention, usual care (± placebo) or a waiting list control. Such choices should reflect the intent and design of the trial (explanatory or confirmatory; hypothesis generating or testing), as reflected in the research question, hypotheses, aims and objectives, and the nature of the placebo and contextual effects the trialists wish to control for.[54] Guidance to aid CRPS trialists in the development, selection and implementation of their comparator and control groups are available.[44,54,90]

Our patient insight partners highlighted the need for CRPS trialists to consider, in partnership with patient representatives, the duration of comparator interventions as trial participants are unlikely to want to receive placebo interventions for protracted periods of time. This consideration may inform the choice of trial design since the duration of placebo periods varies between them.

3.6.2 Reporting

Systematic reviews of interventions for CRPS show that trialists do not always fully describe their index and comparator interventions.[131,158] In response, CRPS trialists should fully report the details of their interventions in accordance with the Template for Intervention Description and Replication (TIDieR) guideline[87] and/or other guidelines as appropriate, such as the Recommendations for the development, implementation, and reporting of control interventions in efficacy and mechanistic trials of physical, psychological, and self-management therapies (the CoPPS Statement)[90] or the Consensus on Exercise Reporting Template (CERT).[157] Reporting the nature, known or hypothesised mechanisms of effects and parameters of trial interventions thoroughly is essential for enabling trial interpretability and replicability.

3.7 Optimising trial outcomes and follow up

CRPS trialists should follow specific Consolidated Standards of Reporting Trials (CONSORT) Outcomes 2022 Extension guidance for defining and justifying trial outcomes, follow-up timepoints, and the target difference between treatment groups used to determine sample size estimates when planning their outcomes of interest. In addition, CRPS trialists should fully report their findings for all prespecified outcomes and time points, regardless of the nature and direction of results.[20]

3.7.1 Endpoints

We recommend that CRPS trialists select clinical end-points informed by the Core Outcome Measurement Set For Complex Regional Pain Syndrome Clinical Studies (COMPACT).[70] CRPS trialists should also consult with their own patient partners to ensure that the COMPACT is applicable to them and to consider other potential outcomes of interest. We appreciate that outcomes of interest will vary according to a trials aims (e.g. explanatory, pragmatic, mechanistic, feasibility). We also acknowledge the challenge of selecting one primary outcome for a complex and multidimensional condition such as CRPS (e.g., changes in pain intensity versus function versus quality of life). Trial teams should therefore consider which dimension of the CRPS experience the intervention is targeting when choosing their primary endpoint. Our patient insight partners highlighted the importance of and measuring quality of life (QoL) since QoL may improve when pain intensity does not.

Also, selection, analysis and interpretation of outcomes depends on the research question and design. Confirmatory trials require that a primary endpoint be defined *a priori*, and this should be the focus of the trial and the analysis. For confirmatory trials of interventions for rare conditions such as CRPS it may be advisable to avoid co-primary endpoints (when it is necessary to demonstrate 'significant' effects on all pre-specified endpoints to conclude that an intervention is effective), as the power of a study is normally reduced by the requirement to demonstrate significant effectiveness of more than one endpoint, unless those endpoints are highly correlated.[121]

CRPS trialists using multiple primary endpoints (when it is necessary to demonstrate a 'significant' effect on any one of a number of pre-specified endpoints to conclude that an intervention is effective), should consider and report their methods for adjusting for multiple comparisons in the analysis.[171] Options for handling multiple endpoints in general and rare disease clinical trials have been described and should be carefully considered.[53,147]

Importantly, CRPS trialists should clearly pre-specify their primary, secondary and other (e.g. exploratory) outcomes in accordance with the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) guidelines,[23] in order to guard against selective outcome reporting and outcome switching. We caution CRPS trialists not to present or interpret an exploratory analysis as confirmatory based on favourable results. Also, we recommend that more sensitive, i.e. continuous rather than binary endpoints should be selected in order to optimise a trial's statistical power.[12] We acknowledge that some CRPS trialists may elect to report some binary outcomes, such as how many patients meet a threshold of change, but it is our opinion that these should be reported as secondary outcomes in addition to, rather than instead of, continuous outcomes.

3.7.2 Adverse events/effects

The definition and reporting of adverse events/effects (AEs) in CRPS trials is known to be inadequate, prohibiting evaluations of intervention safety.[48] Future CRPS trialists should plan (*a priori*) and report their methods for measuring AEs in accordance with the SPIRIT[23] guideline and CONSORT Harms extension.[100] An additional guideline, 'Common Terminology Criteria for Adverse Events' (CTCAE), designed for use in cancer trials,[168] could be adapted for use by CRPS trialists.

CRPS trialists should be aware that AE data are influenced by the methods used to elicit it, and that passive measurement methods may lead to under-detection and reporting of AEs compared to active methods.[3]

3.7.3 Follow up

Follow up time points for outcomes of interest, including safety, are likely to vary according to characteristics of the trial population (e.g. acute or chronic) as well as the purpose of the study and the research question. We propose that the duration of follow-up should be informed by the nature of the intervention and its goals. When trialling interventions that are predicted to have longer-term effects, our group recommends a minimum of six months follow up. Ultimately, length of follow-up should be determined in collaboration with patient and clinical stakeholders. We also recognise that it can be challenging to secure funding to facilitate longer term follow-up of trial participants.

3.8 Optimising data analysis

3.8.1 Statistical analysis plans

Best practice necessitates that trialists should generate a statistical analysis plan (SAP), with their team's biostatistician, in which they report their analysis approach (e.g. intention-to-treat) and planned statistical methods for analysing primary and secondary outcomes, and any additional analyses (e.g., exploratory, subgroup adjusted analyses or interim) in accordance with the SPIRIT guideline.[23] Doing so helps to ensure the interpretability and credibility of trial results and guards against reporting post hoc hypotheses and analyses as if pre-planned.[34]

We recommend that CRPS trialists publish their SAP as part of the trial protocol, a fully published article or in an open access forum such the OSF.[81] Guidelines for the content of SAPs for early and late phase trials are available to assist CRPS trialists.[56,91]

We recognise that SAPs may evolve during the trials lifecycle where trialists might initially outline a preliminary SAP in a funding application before proceeding to writing a full SAP before (open label trials) or during (double blind trials) data collection but prior to undertaking data analyses.

3.8.2 Managing missing data

Missing data can introduce bias in the estimates of treatment effects but is unavoidable in many clinical trials of interventions for pain.[83] In the first instance, CRPS trialists should design their trial to minimise missingness by employing strategies to optimise participant retention and data capture. Following this, CRPS trialists should clearly define and justify their methods for managing missing data (e.g., imputation methods, sensitivity analyses). We recommend that CRPS trialists report their methods for managing missing data as part of their SAP in accordance with published recommendations.[56]

3.8.3 Methods of analysis

'Intention-to-treat' (ITT), whereby participants are analysed according to the treatment group to which they were originally assigned, is the preferred approach to analysis because it maintains randomization (i.e. comparability of groups at baseline with respect to measured or unmeasured prognostic factors).[83] Strategies for handling missing data can be employed to facilitate ITT analyses but these should be determined and reported *a priori*. CRPS trialists should be aware of the biases introduced from alternative methods of analysis that involve selectively excluding participant data and clearly report and justify any modifications to or deviations from ITT (e.g. modified ITT, 'complete case', 'as treated' or 'per protocol') since their use varies greatly between trials and will alter the interpretability of results.[1] A recently updated Cochrane systematic review of physiotherapy interventions for CRPS showed that the majority of trials (53%) did not report their analysis method and 26% violated the ITT principle.[158] These findings suggest that CRPS trialists could improve their application and reporting of ITT. The estimands framework may usefully help trialists specify their analysis strategy.[101]

3.8.4 Covariates

Covariates (i.e. measurable characteristics of a trial population that have a statistical relationship with the outcome variable, e.g. demographic factors, disease characteristics) can be managed at the i) design (when determining the required sample size by using covariate-adjusted estimators), ii) recruitment (through stratified randomisation) or iii) analysis (through statistical adjustment) stages.[169] Statistical adjustment may be preferable as approaches for determining covariate-adjusted estimators are not straightforward and stratification on more than a few covariates is often not feasible due to small sample sizes within strata.[43]

Adjusting for baseline prognostic covariates in the analysis of trials enhances statistical efficiency. Accounting for the variance in (continuous) outcomes explained by covariates reduces standard errors for the treatment effect and minimises the sample size required.[103] Selecting which covariates to include in the analysis of CRPS trials should be based on data from previous trials on similar patient populations or clinical observations of factors known or expected to have strong or moderate associations with the primary outcome.[111,141] For pain trials in general, baseline prognostic covariates could include demographic (e.g. age, sex, ethnicity, workplace compensation claims), pain (e.g. pain intensity or duration), psychological (e.g. depressive symptoms) or cognitive (outcome expectation) factors.[111] Potential biological and psychological prognostic factors in recently diagnosed CRPS, based on moderate quality evidence, include: baseline pain intensity, self-rated disability, anxiety, depression, catastrophising and pain-related fear, female sex and a history of a high-energy triggering event.[16,115] These could be considered as candidate baseline prognostic covariates by future CRPS trialists.

It is critical that covariates are pre-specified for the primary analysis, appropriately justified and not selected and adjusted for post hoc, which could compound the risk of false positive conclusions.[111,141] The number of covariates used should be limited relative to the usually small/modest sample sizes in

CRPS trials. Including non-prognostic covariates may reduce trial power and has been discouraged.[103]

3.8.5 Sensitivity analyses

CRPS trialists may undertake sensitivity analyses to evaluate the extent to which results are robust to different assumptions (e.g. different methods of analysis, protocol deviations, outliers). Sensitivity analyses should be carefully selected, justified and reported within the trial protocol, and any post hoc analyses should be clearly identified as such.[163] Strategies for handling missing data should always include sensitivity analyses.

3.9 Optimising openness, transparency and reporting

3.9.1 Pre-registration, protocol publication and 'registered reports'

A recently updated Cochrane systematic review of physiotherapy interventions for CRPS found that 63% of trials conducted between 2015 and 2021 were either not pre-registered or associated with a published trial protocol.[158]

Pre-registration enhances transparency and credibility and likely reduces potential bias, arising from practices such as outcome switching (changing which outcomes to report or emphasise), p-hacking (analysing data to find statistically significant results) and HARKing (hypothesising after the results are known).[21] It is a mandatory prerequisite for publication in many journals[33,172] and a number of (inter-)national trial registries are available to trialists.

Given the potential bias associated with unregistered trials and trials without published protocols or SAPs, we strongly recommend that all future CRPS trialists register their trials and publish a trial protocol. The SPIRIT guideline provides clear direction for reporting trial protocols.[23]

Future CRPS trialists might also consider publishing a 'registered report' whereby a decision to publish the manuscript is made based on peer review of the research question and the rigorousness of the methods before the trial is undertaken and the results are known. The journal then commits to publishing the study irrespective of the findings. Advantages of guaranteeing publication independent of the trial's outcome include countering perceived pressure to publish 'positive' or novel findings (p-hacking and HARKing) and publication bias.[82]

Prospective pre-registration, protocol publication and registered reports allows others to access essential information concerning a trial's original design, aims and methods against which subsequent trial reports can be compared and verified.[164] They may also reduce research waste and enhance reproducibility.[172]

3.9.2 Sharing materials, code and data

In accordance with open science/research practices we encourage CRPS trialists to share, as far as is legally and ethically feasible, trial materials (e.g. documentation and guides). Once data have been collected, analysed and reported, we encourage trialists to share their analysis code and individual-participant data as well as making their data Findable, Accessible, Interoperable and Reusable (FAIR).[176] Sharing such materials facilitates transparency, reproducibility and secondary analyses, and by extension credibility. Infrastructure to enable such sharing is widely available.[35]

3.9.3 Reporting standards

Existing overviews and reviews of trials for CRPS [48,131,158] demonstrate that existing methodological reporting guidelines, such as, SPIRIT,[23] TIDieR,[87] and CONSORT[148] are not consistently used.

The 'Enhancing the Quality and Transparency of Health Research' (EQUATOR) Network provides numerous guidelines and checklists for reporting clinical trials. These encompass different designs (e.g. factorial trials), methodological features (e.g. use of patient-reported outcomes) and interventions (e.g. social and psychological interventions) as extensions and variations to the standard CONSORT guideline for reporting parallel group randomised trials.[125] A reporting and reviewing checklist specific to pain clinical trials is also available.[59]

We recommend that trialists both plan their trials and report their findings in accordance with guidelines relevant to their trial design and methods as doing so provides the transparency necessary for others to i) critically appraise and interpret findings, ii) replicate the trial and iii) consider implementing its findings.[22] CONSORT guidelines have been endorsed by numerous medical journals and trialists can expect to be required to adhere to them for trial reports.

Our group also highlighted the importance of transparently reporting the nature and potential impact of any deviations from the trial protocol.[161]

3.9.4 Reporting uncertainty

Researchers have been encouraged to accept, measure and communicate uncertainty.[174] However, evidence syntheses show that CRPS trialists inconsistently report results, including effect sizes and statistical measures of uncertainty and precision (e.g. standard deviation, confidence intervals, sensitivity analyses).[131,158] Our group highlighted the need for CRPS trialists to fully report these data and interpret and communicate their findings in light of these uncertainties. Doing so allows others to interpret a trial's findings in light of those uncertainties. A procedure for summarizing scientific uncertainty in the context of clinical trials has been described that CRPS trialists and others might follow.[50]

3.9.5 Narrative bias ('Spin')

Narrative bias refers to misrepresentation of a trial's findings in a way that misleads readers to view results as being more favourable (or unfavourable) than is justified by the data.[60] In the first instance, authors are responsible for avoiding spin; the peer review and editorial process should also explicitly check that trials are reported in a manner consistent with the data. Evidence for spin in pain-related clinical trials has been reported, such as emphasising within-group improvements rather than primary between-group comparisons.[60,128,165] The extent and nature of narrative bias within CRPS trial reports specifically is not known but could be investigated. We strongly recommend future CRPS trialists report their findings objectively and without spin.

Discussion

This methodological framework presents a range of strategies for optimising the planning, design, conduct and reporting of clinical trials of interventions for CRPS. It reflects and builds upon evolving general,[177] pain and rare condition-based methodological knowledge and recommendations by providing clear flexible guidance that specifically addresses the challenges of undertaking clinical trials for CRPS as a rare pain condition. It is offered as a tool to support the CRPS research community to undertake high quality clinical trial research to better guide clinical practice.

Uncertainties underlying the findings from many previous trials of interventions for CRPS arising from insufficiently planned, designed, conducted and reported trials[48,131,158], and from small sample sizes owing to the rarity of the condition, indicates that the scientific quality and efficiency of trial methods could be improved. Methodologically flawed trials that do not meaningfully contribute to the evidence base wastes valuable research resources, delays discovery and implementation of treatments and may ultimately harm trial participants.[127] It is not our intention to complicate or obstruct clinical trials for CRPS but to propose solutions to the numerous complexities and challenges of undertaking such trials in order to improve their rigor and value. Our framework presents a range of solutions and options for optimising the rigorousness and efficiency of CRPS trials.

A fundamental aspect of trial methodology that runs throughout our framework is the optimisation of open science practices as a means to enhance the transparency, quality and reproducibility of CRPS trials. We recommend that CRPS trialists plan, design, implement and report their trials in accordance with open science practices, such as preregistration, registered reports, code sharing, making data FAIR, use of reporting guidelines, including reporting protocol deviations and conflict of interest statements, open access publishing and providing plain language information to non-specialists.[22,113,145,176] Cashin et al. 2021[22] found evidence of limited engagement with transparent and open science standards in the policies of pain journals. The adoption of open science practices in pain research more broadly, or CRPS trials specifically, has not to our knowledge been audited but has been found to be consistently low in surgical and general medicine research[137,162] and is unlikely to be any different in pain research. Promoting, incentivising, adopting and tracking open science practices will require the cooperation of researchers, institutions and journals.[25]

Although this methodological framework was developed primarily as an aid for CRPS trialists it may also benefit peer reviewers and journal editors, funders of CRPS trials, CRPS clinical guideline developers, clinicians and those with lived experience of CRPS when considering publishing, funding, supporting or using the findings from future trials. For the same reasons our framework may be useful to stakeholders within the rare disease community also. Furthermore, since many of the methodological issues and challenges associated with undertaking and optimising clinical trials involving rare pain conditions are also applicable to pain trials in general this framework may be useful to the pain trial community more broadly.[146]

It remains to be seen if and how this methodological framework is implemented by CRPS trialists and others. Methodological frameworks can be refined and validated by undertaking evaluations of their real-world utility.[122] Evolving knowledge and understanding of general, pain and rare condition trial methods together with any subsequent feedback from the pain, CRPS and rare disease communities will likely necessitate the revision of this methodological framework in the future.

We have endeavoured to provide guidance based on the collective knowledge and expertise of an interdisciplinary international group of CRPS, rare condition methodology and biostatistics, evidence synthesis and patient experience experts; informed by and with reference to best practices. However, our white paper should be interpreted in light of a number of potential limitations. We acknowledge that there is no single best or standardised approach for developing methodological frameworks and that this paper represents the collective opinions of one purposefully sampled group. A different, more geographically diverse group of individuals, using similar or different methods may have generated alternative perspectives, opinions and recommendations.

It is our hope that optimising trial methods in CRPS will improve the quality of the evidence upon which clinical decisions and guidelines for the management of CRPS are based, and in doing so, optimise outcomes for people living with CRPS.

Declarations of interest

KMS has received financial support from the European Pain Federation (EFIC) to attend congresses of the European Pain Federation (EFIC).

SB has received research grant funding through the U.S. National Institutes of Health and is a consultant for Akigai.

SD has received research grants from the European Commission and travel bursaries from the European Commission and National Institutes of Health. In addition, SD works as a consultant to the pharmaceutical industry.

DJK's institution receives research grants from the National Institute for Health and Care Research (NIHR).

NEO is a member of the Cochrane Central Editorial Board. Between 2020 and 2023 NEO was Co-ordinating Editor of the Cochrane Pain, Palliative and Supportive Care group, whose activities were funded by an infrastructure grant from the UK National Institute of Health and Care Research (NIHR). He currently holds a networking grant from the ERA-NET Neuron Co-fund.

All other authors (VAF, FB, EC, SG, R-DH, CI, FK, CM, SN) declare no conflicts of interest.

Patient and Public Involvement and Engagement Statement

Two patient insight partners (VAF and EC) with lived experience of CRPS contributed their knowledge and expertise and ensured that the perspectives of people living with CRPS were included in this methodological framework. We hope that people living with CRPS who are invited to participate in future clinical trials feel empowered enough to question trialists about the quality of their research methods.

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Appendix 1:
OptiMeth-CRPS methodological framework ‘cheat sheets’

Optimising Clinical Trial Methods For COMPLEX REGIONAL PAIN SYNDROME

OptiMeth | CRPS
OPTIMISING CLINICAL TRIAL METHODS FOR COMPLEX REGIONAL PAIN SYNDROME

PLANNING

1 Trial Team

▶ Ensure appropriate trial expertise
☐ Clinical
☐ Scientific
☐ Methodological & biostatistical
☐ Lived experience

▶ **Develop and implement a Public & Patient Involvement & Engagement (PPIE) strategy**
☐ Include people with lived experience of CRPS & CRPS-advocacy groups
☐ PPIE expertise can enhance the quality of clinical trials
☐ Allocate adequate financial resources to facilitate PPIE

2 Research Question

▶ **Carefully develop & state the research question**
☐ Formulate research question a priori, in order to focus the trial's purpose
☐ Make clear distinctions between exploratory (hypothesis generating) and confirmatory (hypothesis testing) trials
☐ Express the hypothesised relationships between the variables under investigation

▶ **Clearly position the trial along the pragmatic/ explanatory design continuum**
☐ State a priori whether the purpose of the trial is to investigate the efficacy (explanatory trial), or effectiveness (pragmatic trial) of an intervention

3 Trial Governance & Management

▶ **Implement trial management systems**
☐ Implement trial management systems for planning, conduct & quality

▶ **Establish governance committees**
☐ Set up trial steering & data monitoring committees

DESIGNING

4 Trial Design

▶ **Consider trial design options for rare conditions & CRPS**
☐ Explain & justify choice of trial design
☐ Ensure consistency with research question
☐ Acknowledge associated assumptions & limitations within the trial protocol

Approach to be used in most situations
☐ Conventional parallel trial designs

Approaches to be used with caution & guidance
☐ Crossover trials & N-of-1 trials designs
☐ Factorial trial designs
☐ Randomised withdrawal designs
☐ Adaptive trial designs

▶ Consider single versus multicentre trials, or decentralised trials

Single Centre Trials

Advantages
☐ Logistically simpler to conduct
☐ Less resource intensive
☐ Appropriate for testing new interventions

Limitations
☐ Reduce the generalisability of results
☐ Are associated with larger estimates of treatment effects compared to multicentre trials

Multicentre trials

Advantages
☐ Help achieve sample size requirements
☐ Enhance the generalisability of findings

Limitations
☐ Challenging to conduct, coordinate & manage
☐ Resource intensive
☐ Require protocol adherence, quality assurance & data management

Decentralised trials

Advantages
☐ Enable broader equity of access & reduce participant burden
☐ May improve participant enrolment, engagement & retention

Limitations
☐ Present safety, privacy & scientific validity challenges
☐ May require methodological modifications to the application of diagnostic eligibility criteria, selection of outcome measures or nature of the interventions tested

DESIGNING

4 Trial Design

▶ Select appropriate randomisation procedure

☐ Select randomisation procedure appropriate to the research question & characteristics of the trial

▶ Use observational designs & data cautiously

☐ Potential biases & likelihood of confounding are larger when compared with randomised trials

☐ Be clear about the limitations imposed by such designs when interpreting data & drawing conclusions

☐ Consider as exploratory & hypothesis generating rather than confirmatory

▶ Use registry data appropriately

Useful for

☐ Estimating parameters to inform sample size estimates & meaningful endpoints

☐ Generating hypotheses about subgroups

5 Trial Population

▶ Ensure equality, diversity & inclusivity in CRPS trial recruitment

☐ Ensure that no one living with CRPS is excluded from participation due to language, logistical or cultural barriers

☐ Design & implement inclusive recruitment strategies

▶ Describe & justify diagnostic eligibility criteria

☐ Use Budapest diagnostic criteria

☐ Any modifications to diagnostic eligibility criteria may depend on where the research question is located on the pragmatic/explanatory continuum

▶ Carefully plan & define any approach to subtyping/phenotyping

☐ Subtypes of CRPS have been explored & described based on hypothesised variations in pathophysiological mechanisms

☐ Evidence for the validity of subtypes of CRPS is not yet sufficient to justify their use in confirmatory (hypothesis testing) clinical trials

CONDUCTING

6 Interventions & Comparator Groups

▶ Justify the intervention & comparator

Systematically evaluate existing data on efficacy & effectiveness to

☐ Justify the selection of the index & comparator interventions

☐ Inform intervention parameters (components, dosage, mode of delivery)

☐ Avoid unnecessary replication & research waste

▶ Report details of index & comparator interventions

☐ Fully report the nature, parameters & known or hypothesised mechanisms of effects of trial interventions

7 Trial Outcomes & Followup

▶ Pre-specify & define all trial endpoints

☐ Define primary endpoint a priori, this should be the focus of the trial & the analysis

☐ Select clinical endpoints based on core outcome measurement guidelines & in consultation with patient partners

☐ Consider which dimension(s) of CRPS experience are being targeted (such as pain intensity, disability, quality of life, etc.)

▶ Measure adverse events/effects

☐ Plan & report methods for capturing adverse events/effects

▶ Define & justify follow-up

Follow-up time points should be

☐ Informed by the nature & goals of the intervention

☐ Determined in collaboration with patient representatives

☐ Interventions predicted to have longer-term effects require a minimum of six-month follow-up

CONDUCTING

8 Data Analyses

▶ Generate a statistical analysis plan
☐ Generate & publish a Statistical Analysis Plan (SAP) as part of the trial protocol in conjunction with a biostatistician
☐ Plan statistical methods for analysing primary & secondary outcomes & any additional analyses (e.g., exploratory, subgroup, adjusted analyses or interim)

▶ Define & justify methods for managing missing data
☐ Minimise missingness by employing strategies to optimise participant retention & data capture
☐ Report methods for managing missing data as part of the SAP

▶ Pre-specify the methods of analysis
☐ 'Intention-to-treat' (ITT) preserves randomisation & is the preferred approach
☐ Clearly report & justify any modifications to or deviations from ITT
☐ Be aware of the biases introduced from other methods of analysis that selectively exclude participant data from the analysis

▶ Pre-specify covariates & how they will be managed
☐ Pre-specify covariates for the primary analysis a priori
☐ In design phase, use covariate-adjusted estimators when determining sample size
☐ Or in recruitment phase, manage covariates through stratified randomisation
☐ Or in analysis stage, manage covariates through statistical adjustment (likely to be the preferred approach)

Baseline prognostic covariates could include the following variables
☐ Demographic (age, sex, ethnicity)
☐ Pain (intensity or duration)
☐ Psychological (depressive symptoms)
☐ Cognitive (outcome expectation)

▶ Select, justify & report sensitivity analyses
☐ Undertake sensitivity analyses to evaluate the extent to which results of primary analyses are robust to different assumptions (such as different methods of analysis, protocol deviations)
☐ Select, justify & report in the trial protocol

REPORTING

9 Openness, Transparency & Reporting

▶ Preregister the trial & publish a trial protocol or registered report
☐ Pre-registering trials enhances trial transparency & credibility & reduces potential bias
☐ Pre-registration is a mandatory prerequisite for publication in many journals
☐ Publish a trial protocol transparently detailing how the trial will be conducted
☐ Consider publishing a 'registered report'

▶ Share materials, code & data
Follow open science/research practices
☐ Share trial materials - analysis code & individual-participant data
☐ Make data Findable, Accessible, Interoperable and Reusable (FAIR)

▶ Follow reporting standards
☐ Plan & report findings in accordance with guidelines relevant to trial design & methods
☐ Report the nature & potential impact of any deviations from the trial protocol

▶ Report & interpret measures of uncertainty
☐ Report effect sizes & statistical measures of uncertainty & precision (e.g. standard deviation, confidence intervals, sensitivity analyses)

▶ Avoid narrative bias ('Spin')
☐ Report findings objectively & without spin


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OPTIMISING CLINICAL TRIAL METHODS FOR
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