

What is the content of virtually delivered pain management programmes for people with persistent musculoskeletal pain? A systematic review

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Abstract

Introduction: Virtual consultations (VC) have been embraced by healthcare organisations during the COVID-19 pandemic. VC allows continuation of patient care while adhering to government advised restrictions and social distancing measures. Multidisciplinary pain management programmes (PMPs) are a core element of many pain services and utilising virtual methods to deliver PMPs has allowed them to continue to provide care. This systematic review aimed to explore the content of existing virtually delivered PMPs and discuss if and how these findings can be used to guide clinical delivery.

Methods: Eligible studies included adults (aged ≥18 years) with persistent musculoskeletal pain and any virtually delivered intervention that was described as a PMP or that had components of PMPs. Databases were searched from inception until July 2020. We performed a content analysis comparing existing interventions with established evidence-based clinical guidelines published by the British Pain Society (BPS). Intervention reporting quality was assessed using the Template for Intervention Description and Replication (TIDieR) checklist: an established checklist developed to improve the completeness of the reporting of interventions.

Results: Eight studies were included. One intervention included six of the seven components recommended by the BPS; none included all seven. 'Skills training and activity management' was present in all eight interventions; 'education' and 'cognitive therapy methods' were present in six interventions; 'graded activation' and 'methods to enhance acceptance, mindfulness and psychological flexibility' were present in four interventions; 'physical exercise' was present in two interventions and 'graded exposure' was present in one intervention. None of the studies described all 12 items of the TIDieR checklist adequately enough for replication.

Conclusion: Published virtual PMPs partially meet established clinical guidelines. Future virtual PMPs should be based on evidence-based clinical guidelines, and more research is needed to explore the effectiveness of virtually delivered PMPs and each recommended component.

Keywords

COVID-19, chronic pain, persistent pain, pain management programme, rehabilitation, virtual consultations

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Introduction

The COVID-19 pandemic has led to significant disruption of services providing multidisciplinary pain management. The cessation of treatment for people with persistent pain will have consequences for service users and healthcare providers as the number of people requiring pain management services and the complexity of their problems will increase.2 Reduced access to assessment and treatment can lead to increased severity of symptoms² which will add to the high prevalence of persistent pain across Europe.³ People with persistent pain are at more risk of being critically ill with COVID-19 and are more likely to be self-isolating in order to reduce their chances of being infected.4 Research has shown that people with persistent pain suffer greater adverse effects of 'lockdown'.4 This may lead to self-perceived increases in pain, greater increases in anxiety and depression, increased loneliness and reduced physical activity.4 Consequences of reduced physical activity and greater stress increase the chance of physical deconditioning⁵ and risk of sarcopenia,6 which is associated with a number of other chronic health conditions. Reduced access to multidisciplinary pain management services is likely to increase the burden on healthcare.6

Virtual consultations (VC) have been embraced by healthcare organisations in order to continue to provide patient care while complying with government advised social distancing measures. VC is one potential way to continue to provide pain services to patients during the pandemic^{2,5} and has been demonstrated to be accurate, cost-effective and safe, 8-12 and has high satisfaction among patients due to convenience, absence of travel time and reduced time off work. 12

Pain management programmes (PMP) consist of methods to promote behaviour change and enhance well-being. ¹³ They aim to enable people with persistent pain to live as normal a life as possible by improving an individual's ability to reduce and self-manage pain-associated disability and emotional distress. ¹³ PMPs can be effective at reducing pain interference, ¹⁴ pain intensity, ^{15,16} disability ¹⁶ and distress. ¹⁶ The British Pain Society (BPS) has published evidence-based clinical guidelines for PMPs in adults. ¹³ There is currently no guidance for delivering PMPs virtually.

A recent rapid review¹⁷ presented a number of issues to consider when using VC to deliver group-based pain rehabilitation. These include issues with inclusion, access, participation, attrition, infrastructure, clinician training and confidence, and evaluation. Systematic reviews of the literature are important summaries of existing evidence to help inform changes to practice; to our knowledge, there are no systematic reviews discussing or evaluating virtually delivered PMPs. We

therefore conducted a systematic review of the literature to identify studies reporting the use of VC in PMPs. This systematic review aims to explore the content of existing virtually delivered PMPs that include real-time delivery and discuss if and how these findings can be used to guide clinical delivery of virtual PMPs.

Methods

This review has been reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement. This review was submitted in July 2020 and registered with the International Prospective Register of Systematic Reviews (PROSPERO: CRD42020201593) on the 25 August 2020.

Search strategy

A list of search terms combining keywords and Medical Subject Headings (MeSH) terms was developed by the authors. Search terms related to chronic/persistent pain, pain management and telemedicine and were combined using the Boolean operators. We searched four databases: CINAHL, MEDLINE, PsycINFO and AMED which were chosen due to their widespread coverage of clinical research topics. The search was completed by one author (A.W.G.) on 21 July 2020. We also searched the reference lists of similar systematic reviews for additional articles. Supplementary Material 2 presents the search strategy for each database.

Study selection and eligibility criteria

Search results were exported into Endnote¹⁹ and duplicates were removed. Remaining titles and abstracts were imported into Microsoft Excel for screening. Next, all titles and abstracts were screened against the eligibility criteria. One author (A.W.G.) screened 100% of the titles and abstracts, one author screened 50% (G.B.) and two authors screened 25% each (D.W. and H.P.) to ensure all titles and abstracts were independently screened by two authors. To ensure consistency, the eligibility criteria were discussed between all authors prior to starting the title and abstract screening to resolve any uncertainties. Furthermore, all authors referred to the eligibility criteria throughout and further uncertainties that arose were discussed with all authors at the nearest opportunity. Of the remaining articles, two authors (G.B. and A.W.G.) reviewed full texts and agreed on the included articles. Any ambiguities in the screening process were resolved by discussion with a third author (D.W.).

Studies of interest were those that consisted of adults (aged ≥ 18 years) with persistent musculoskeletal (MSK) pain; defined as pain lasting ≥ 3 months,²⁰

that is, experienced in bones, joints, muscles, tendons and other related soft tissues.²¹ There were no restrictions to the specific conditions or origins of persistent MSK pain. Studies were included if they contained participants with persistent MSK pain, even if participants with other origins of pain were also included. We included any study with an intervention that was described as a PMP, a pain rehabilitation programme, or that had components that were consistent with PMP clinical guidelines, 13 that was delivered virtually/ remotely in real time (e.g. via telemedicine). This included multi-component interventions as long as part of the intervention met this criterion. There were no limitations to study design. Studies of interest were published in peer-reviewed journals and had to be in English language. Papers reporting interventions where none of the components were aimed at active self-management of pain (such as prescription of medications/advice giving on medications) were excluded.

Data extraction

Three authors (G.B., H.P. and D.W.) independently extracted the data using a data extraction table that was created based on the data sought in this study. One author (A.W.G.) reviewed all the data extraction for accuracy. Extracted data included study design, number of participants, participant characteristics (age, sex, ethnicity and conditions/pathologies), interventions characteristics (treatment approach, specific contents, providers, dose and method of delivery/technology used) and adverse events.

Quality assessment (Template for Intervention Description and Replication)

We completed a Template for Intervention Description and Replication (TIDieR) checklist²² for each study in order to report on the quality of the reporting of interventions. One author (G.B.) completed TIDieR checklists for all studies and a second author (A.W.G.) reviewed these for accuracy.

Data synthesis

We performed a content analysis of each intervention; comparing them with the 'specific cognitive and behavioural methods' components of the established BPS PMP Guidelines for adults. These guidelines provide evidence-based recommendations of what PMPs delivered in healthcare settings should include. The guideline's components include 'graded activation', 'cognitive therapy methods', 'graded exposure', 'methods to enhance acceptance, mindfulness and psychological

flexibility', 'skills training and activity management', 'physical exercise' and 'education'. Reference to the definitions used in the guidelines was referred to throughout this analysis to maximise accuracy.

Results

Study selection

The search yielded a total of 1514 results, and 1155 unique articles were remaining after duplicates were removed. Of these, 1130 were excluded after title and abstract screening, leaving 25 articles for full-text review. After reviewing the full texts, eight were included in the systematic review.^{23–30} The PRISMA flow diagram is demonstrated in Figure 1.

Study and participant characteristics

Of the eight included studies, one was a randomised controlled trial (RCT),²⁴ one was a randomised trial (no control),²³ two were non-randomised trials,^{25,28} one was a longitudinal case—control study,²⁶ one had a single-case experimental design,²⁷ one was a retrospective cohort analysis²⁹ and one was a descriptive study.³⁰ Participant characteristics are demonstrated in Table 1.

Intervention characteristics

Table 1 presents intervention delivery methods, dose and schedule. All seven of the specific cognitive and behavioural methods of the BPS PMP guidelines¹³ were present across the studies. The highest number of guideline contents in one study was six²⁴ (Table 2).

Graded activation guided by participant goals. Graded activation guided by participant goals was present in four interventions. ^{24,26,29,30} Goal setting was used in all four of these studies and coincided with physical activity ^{24,26,30} and self-care. ²⁹ 'Relapse prevention', a strategy aimed at facilitating maintenance of change, was present in two of these studies. ^{24,30}

Cognitive therapy methods. Cognitive therapy methods were present in six studies.^{23,24,27–30} They were often described as teaching ways of managing or challenging negative thoughts.^{23,24,28,29} Others simply stated they were using 'cognitive restructuring' methods^{27,30} without further elaboration of the detail of this.

Graded exposure. Graded exposure was described in one intervention.²⁴ It was described as consisting of an explanation on the issues of fear and avoidance of physical activities, and instructions on gradually and safely increasing physical activities.

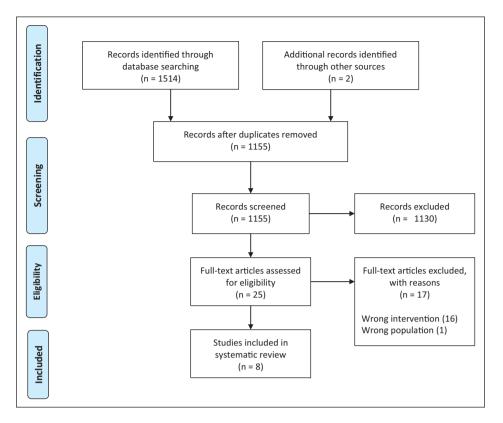


Figure 1. PRISMA 2009 flow diagram.

Methods to enhance acceptance, mindfulness and psychological flexibility. Four studies described methods of enhancing acceptance, mindfulness and psychological flexibility. ^{24,25,28,29} Two of these studies stated using mindfulness techniques^{28,29}; one described monitoring negative thoughts²⁴ and one described exploring behaviours and responses to disability. ²⁵ There were no further explanations of these techniques.

Skills training and activity management. All eight studies included elements of skills training and activity management. Five studies included teaching of relaxation techniques^{24,26–28,30} to alter the adverse effects of thoughts and feelings. Another study stated teaching methods of managing negative emotions, without including specific details.²³ Six studies taught goal setting.24,26-30 Five studies taught activity management or pacing techniques^{24,26-28,30} to balance time spent on meaningful activity or rest. Four interventions included skills for communication and social interaction, 23,27,28,30 with two studies specifically stating teaching assertiveness skills.23,30 Three studies were taught sleep management skills.25,27,28 One study was introduced to self-monitoring techniques.²⁶ In addition to the two mentioned above, two other studies reported teaching 'relapse prevention' skills.27,28 These studies did not elaborate further on specifics of this skill.

Physical exercise. Two studies included physical exercise components.^{25,30} One of these included stretching, strengthening and aerobic exercise³⁰ and the other included training in exercise.²⁵

Education. Six studies included education. 24-28,30 Three of these studies included pain education. 24,26,27 The other studies included education on nutrition, 25 weight management 28 and posture. 30

Control and comparator group characteristics

Three studies had control groups; two of these studies^{24,25} had waitlist controls and the other study compared online group cognitive behavioural therapy (CBT) with in-person group CBT as the control.²⁸ One study monitored symptoms and side effects of control participants.²⁶ Another study had telephone delivered pain education as their comparator to telephone delivered CBT.²³ Three studies did not have control or comparator groups due to their study design.^{27,29,30}

Intervention reporting quality (TIDieR)

TIDieR checklist items one (brief name), two (rationale, theory or goal), three (materials), four (procedures), six

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Table 1. Characte	Table 1. Characteristics of included studies.	ed studies.				
Study and design	Number of participants	Age: mean (SD) (years)	Number (%) female	Conditions/ pathologies	Intervention details	Control/comparator details
Carmody, 2013 ²³ Randomised trial	Total: 101	Total: 67.5	Total: 3 (3%)	Not reported	Name: Telephone-delivered cognitive behavioural therapy (T-CBT) Delivery method: Telephone Individual Dose: 12 sessions over 20 weeks Schedule: Weekly - first eight sessions Fortnightly - next two sessions	Type: Comparator Description: Telephone- delivered education (T-EDU)
Dear, 2015 ²⁴ <i>RCT [4-arm]</i>	Total: 490	Total: 50 (13)	Total: 375 (80%)	Pain locations: Head/facial Neck Shoulders Upper limb Lower back Pelvic/sacrum Lower limb	Name: The Pain Course: Internet-delivered PMP based on CBT Delivery method: Online lessons Lesson summaries Homework tasks Real-time contact: phone or email with a psychologist No tailoring Dose: Five online lessons Five lesson summaries Real time: Regular contact = 10-15 minutes weekly Optional contact = 10-15 minutes sessions Schedule: 1 week between lessons 1 and 2, and 3 and 4 2 weeks between lessons 2 and 3, and 4 and 5	Type: Control Description: Waiting list

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Study and design	Number of participants	Age: mean (SD) (years)	Number (%) female	Conditions/ pathologies	Intervention details	Control/comparator details
Gardner-Nix, 2012 ²⁵ <i>Non-randomised</i> <i>trial</i>	Total:	Total: 52 (range = 32- 79)	Total: 90 (76%)	Back pain Fibromyalgia Facial pain Arthritis Neck pain Shoulder pain Chest pain Migraine Multiple sclerosis Neuropathy Crohn's disease Leg pain	Name: Mindfulness-based chronic pain management programme [MBCPM] – modified MBSR (stress reduction) Delivery method: Videoconferencing and face-to-face combination simultaneously Class-sizes of 12–22 (combined on-site and offsite) Dose: 12 sessions in 12 weeks Schedule: Weekly	Type: Control Description: Waiting list
Helstrom, 2018 ²⁶ Longitudinal case-control study	Total: 160	Total (all eligible participants): 76.7 (7.1)	Total (all eligible participants): 198 (79.2%)	High symptom chronic pain (pain interference 8+)	Name.' Pain Care Management (PCM) Delivery method: Telephone Individual Tailored Dose: 20 minutes sessions Five treatment sessions in 3 months Three maintenance calls Schedule: Treatment: weeks 2, 4, 6, 9 and 12 Maintenance: weeks 16, 20 and 24	Type: Control Description: Symptom monitoring
Lafontaine, 2018 ²⁷ <i>Single-case</i> <i>experimental</i> <i>design</i>	Total: 2	Total: 63	Total: 2 (100%)	Fibromyalgia Peripheral neuropathy	Name: CBT for chronic pain Delivery method: Videoconference Individual by a psychologist or doctoral student in psychology Tailored Dose: 10-13 1-hour sessions Schedule: Weekly	N/A

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Study and design	Number of participants	Age: mean (SD) (years)	Number [%] female	Conditions/ pathologies	Intervention details	Control/comparator details
Mariano, 2019 ²⁸ Non-randomised trial	Total: 93	Total: 57.1	Total: 61 [65.6%]	Chronic low back pain (CLBP)	Name: Group CBT teletherapy for chronic pain Delivery method: Online group CBT Individual follow-up calls Eight per group Not tailored Dose: Eight sessions Schedule:	Type: Control Description: In person group PMP
Mochari- Greenberger, 201 <i>7²⁹</i> <i>Retrospective</i> <i>cohort analysis</i>	Total: 170	Total: 53.3 (8.9)	Total: 130 [76%]	MSK pain Fibromyalgia Nerve pain Headache	Name: AbleTo – technology-enabled telebehavioural therapy programme for chronic pain – CBT/ACT based Delivery method: Telephone or videoconference Provider: behavioural health provider and behaviour coach Individual Tailored Dose: 45 minutes sessions 15 sessions 8 weeks Schedule: Not reported	N/A
Palyo, 2012 ³⁰ Descriptive study [qualitative]	Not reported	Not reported	Not reported	Veterans with chronic pain	Name: Cognitive behavioural and physical therapy group intervention Delivery method: Videoconferencing Group-based Providers: psychologist and physical therapist Dose: 2-hour sessions 10 weeks Schedule: Not reported	N/A

MBSR: mindfulness-based stress reduction; ACT: acceptance and commitment therapy; SD: standard deviation; PMP: pain management programme.

	Graded	Cognitive	Graded	Methods to enhance	Skills training and	Physical	Education (e.g. pain
Study (first author, year)	activation	therapy methods	exposure	acceptance, mindfulness and psychological flexibility	activity management (e.g. relaxation, pacing and sleep)	exercise	mechanisms/physiology, and pros and cons of medication)
Carmody, 2013		>			>		
Dear, 2015	>	>	>	>	>		>
Gardner-Nix, 2014				>	>	>	>
Helstrom, 2017	>				>		>
Lafontaine, 2018		>			>		>
Mariano, 2019		>		>	>		>
Mochari-Greenberger, 2017	>	>		>	>		
Palyo, 2012	>	>			>	>	>

Table 2. Studies and items of the British Pain Society PMP guidelines

BPS: British Pain Society; PMP: pain management programme. \prime = guideline item present in intervention.

(modes of delivery) and seven (locations) were adequately described in all eight intervention descriptions. Two intervention descriptions did not include sufficient information on who provided the intervention (item five). ^{23,28} One study did not adequately describe the dose or intensity (item eight)²³ that the intervention was delivered at. Three studies did not provide information on whether the intervention was designed to be tailored or not, and under what circumstances (item nine). ^{27,28,30} Seven studies did not mention details of any modifications (item 10) that may have happened during the study. ^{23–26,28–30} Five studies did not report any plans to measure adherence or fidelity (item 11)^{24–26,28,30} and five studies did not report any actual details of adherence or fidelity (item 12). ^{25,26,28–30}

One study adequately described seven of the TIDieR items,²⁸ one study adequately described eight of the items,³⁰ three studies adequately described nine items,^{23,25,26} two adequately described ten items^{24,29} and one adequately described eleven items.²⁷ No studies described all 12 items adequately enough for replication (Table 3).

Adverse events

No studies formally reported any adverse events.

Discussion

To our knowledge, this is the first systematic review to assess the content of virtually delivered PMPs, or interventions including components of PMPs, in accordance with evidence-based clinical guidelines.¹³ We found that all eight of the included interventions had elements of 'skills training and activity management'. 'Cognitive therapy methods' and 'education' were each present in six studies. 'Graded activation guided by participant goals' and 'methods to enhance acceptance, mindfulness and psychological flexibility' were each present in four studies. 'Physical exercise' was present in two studies and 'graded exposure' was only present in one study. None of the included studies included all the components recommended by the BPS guidelines.¹³ None of the studies adequately described all 12 TIDieR items: with details of modifications, fidelity and adherence being the items most commonly lacking. Name, rationale, theory or goal, materials, procedures, modes of delivery and location were adequately reported in all eight studies. No studies formally reported any adverse events.

None of the studies reported using clinical guidelines in their intervention design. 'Cognitive therapy methods' was one of the most common guideline items present across the interventions. CBT is effective (albeit effects are small or very small) at reducing pain and disability, ¹⁶

Table 3. Studies and items of the TIDieR checklist.

Study (first author, year)	Carmody,	Carmody, Dear, 2015		Helstrom,	Helstrom, Lafontaine,	Mariano,	Mochari-	Palyo,
TIDieR checklist item	. 2013		2014	7017	20.18	2019	Greenberger, 2017	2012
1. Brief name	>	>	>	>	>	>	>	>
2. Why (rationale, theory, goal)	>	>	>	>	>	>	>	>
3. Materials used in intervention (physical or informational)	>	>	>	>	>	>	>	>
4. Procedures (activities, processes)	>	>	>	>	>	>	>	>
5. Intervention providers	×	>	>	>	>	×	>	>
6. Modes of delivery (e.g. face-to-face, virtual, individual or group)	>	>	>	>	>	>	>	>
7. Location of intervention	>	>	>	>	>	>	>	>
8. When and how much (number of sessions, time period, schedule and dose)	×	>	>	>	>	>	>	>
9. Details of tailoring	>	>	>	>	×	×	>	×
10. Modifications to intervention	×	×	×	×	>	×	×	×
11. Planned adherence and fidelity assessment	>	×	×	×	>	×		×
12. Actual adherence and fidelity	>	`	×	×	`	×	×	×

TIDieR: Template for Intervention Description and Replication checklist. \checkmark indicates item adequately reported. X indicates item inadequately or not reported.

and at improving multiple psychosocial issues associated with persistent pain. ^{16,31,32} The effectiveness of CBT delivered by videoconference for posttraumatic stress disorder is comparable with face-to-face delivery. ³³ Psychotherapy methods delivered by videoconference, including CBT, can be effective for depressive symptoms ³⁴ and may be for anxiety; ³⁵ highly prevalent problems for people with persistent MSK pain conditions. ^{36,37} This suggests that CBT methods delivered by videoconference may be effective for people with persistent MSK pain and should be included in virtually delivered PMPs.

Patients with persistent non-cancer pain expect explanations or improved understanding of the their pain problem.³⁸ Pain neuroscience education can facilitate a patient's ability to cope with their pain, reduce kinesiophobia and decrease catastrophising.³⁹ The evidence for patient education delivered via real-time virtual methods is lacking but may be feasible⁴⁰ and should be considered for inclusion in virtual PMPs.

Half of the interventions included 'methods to enhance acceptance, mindfulness and psychological flexibility'. Acceptance and mindfulness-based interventions can be effective at reducing pain and psychological problems and can improve physical and mental health-related quality of life in people with persistent pain. 41,42 Studies of stand-alone virtually delivered acceptance and/or mindfulness interventions are lacking in healthcare research; this lack of supporting evidence may be a reason these treatments were not utilised across all studies.

Physical exercise was reported in two studies. Exercise alone delivered via telemedicine has been shown to be better than no intervention.⁴³ A combination of exercise and pain coping skills training delivered by videoconference is effective for pain and function long-term in people with chronic knee pain.⁴⁴ Exercise should be included in virtual PMP's. All eight studies included 'skills training' which could be incorporated with exercise.

'Graded exposure' was present in only one study; this was taught during one online lesson and not practised with the participants. A Reasons for limited inclusion in interventions are unknown, and to our knowledge, there are no studies investigating graded exposure performed via virtual methods for any condition. Considering greater degrees of kinesiophobia are associated with higher pain levels and disability, and lower quality of life and the fact that graded exposure can reduce pain-related kinesiophobia, studies of virtually delivered graded exposure are required to be able to evaluate their effectiveness when working remotely with patients.

Strengths and limitations

These results must be considered in light of the study limitations. There were multiple study designs included and only two of these were randomised trials. We were therefore unable to perform formal quality assessments of the included studies due to variation in the study types as we would be unable make useful comparisons.

This systematic review was prospectively registered on the PROSPERO database, it has been reported in line with PRISMA guidelines¹⁸ and multiple authors were involved at each stage of the review process. We compared existing interventions with established evidence-based clinical guidelines¹³ and we assessed intervention reporting quality with well-known guidance,²² strengthening our analysis. The included studies represented a broad range of chronic pain conditions, with a large number of these MSK in origin and location, although only one study solely focused on MSK pain.²⁸

Implications for research and clinical practice

There is a current lack of high-quality research into real-time virtually delivered PMPs. There is also limited research into real-time virtual delivery of any of the recommended components of these programmes. Future research should address these gaps in order to improve confidence in either programme or individual component effectiveness, which can subsequently be used to guide evidence-based clinical practice. Future research should focus on delivering PMPs that are in-line with established evidence-based clinical guidelines such as the BPS PMP guidelines.¹³ Interventions need to be well reported to enable replication in clinical practice; the use of checklists and tools such as the TIDieR checklist13 can aid this. Studies should also report any adverse effects of virtual PMPs as these are currently unknown, and patient safety remains of high importance. No specific guidance on clinical delivery can be made from this study. Despite the limited evidence for real-time virtual delivery of PMPs, clinical guidelines such as the BPS PMP guidelines¹³ should still be used as a framework when designing virtually delivered programmes, with requirements and resources being tailored to individual context.

Conclusion

The COVID-19 pandemic has interrupted the care of people requiring multidisciplinary pain management for musculoskeletal pain. Virtually delivered PMPs have been cited as a means to continue the delivery of care for people with persistent pain. We have successfully conducted a systematic literature review of studies reporting virtually delivered PMPs. We found that few studies considered best practice guidelines, such as those offered by the BPS during the design of their

programmes. Clinical interventions should be based on evidence-based clinical guidelines and future research should explore the effectiveness and acceptability of each component when delivered remotely.

Conflict of interest

The author(s) declared no potential conflicts of interest with respect to the research, authorship and/or publication of this article.

Contributorship

G.B. and A.W.G. conceptualised and designed the study. G.B. and A.W.G. developed the search strategy. A.W.G. completed the search. G.B., D.W., H.P. and A.W.G. contributed to the screening process and data extraction. G.B. conducted the content analysis. All authors contributed to interpretation of results. G.B. drafted the manuscript. D.W., H.P. and A.W.G. critically revised the manuscript. All authors approved the final version for publication.

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Guarantor

G.B. is the guarantor of this study.

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Supplemental material

Supplemental material for this article is available online.

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