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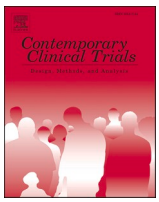

Current practice in the measurement and interpretation of intervention adherence in randomised controlled trials: A systematic review

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ABSTRACT

Background: Ideally all participants in a randomised controlled trial (RCT) should fully receive their allocated intervention; however, this rarely occurs in practice. Intervention adherence affects Type II error so influences the interpretation of trial results and subsequent implementation. We aimed to describe current practice in the definition, measurement, and reporting of intervention adherence in non-pharmacological RCTs, and how this data is incorporated into a trial's interpretation and conclusions.

Methods: We conducted a systematic review of phase III RCTs published between January 2018 and June 2020 in the National Institute for Health Research Journals Library for the Health Technology Assessment, Programme Grants for Applied Research, and Public Health Research funding streams.

Results: Of 237 reports published, 76 met the eligibility criteria and were included. Most RCTs ($n = 68$, 89.5%) reported adherence, though use of terminology varied widely; nearly three quarters of these ($n = 49$, 72.1%) conducted a sensitivity analysis. Adherence measures varied between intervention types: behavioural change ($n = 10$, 43.5%), psychological therapy ($n = 5$, 83.3%) and physiotherapy/rehabilitation ($n = 8$, 66.7%) interventions predominately measured adherence based on session attendance. Whereas medical device and surgical interventions ($n = 17$, 73.9%) primarily record the number of participants receiving the allocated intervention, a third ($n = 33$, 67.3%) of studies reported a difference in findings between primary and sensitivity analyses.

Conclusions: Although most trials report elements of adherence, terminology was inconsistent, and there was no systematic approach to its measurement, analyses, interpretation, or reporting. Given the importance of adherence within clinical trials, there is a pressing need for a standardised approach or framework.

1. Background

While randomised controlled trials (RCTs) remain the optimal study design for evaluating the effectiveness of an intervention; research to understand and improve the design, delivery, and analysis of RCTs is required in tandem [1]. This includes the concept of adherence, or the extent to which participants receive their allocated intervention as intended. Deviations from intended interventions can increase the risk of Type II errors, incorrectly failing to reject the null hypothesis [2], and therefore impact on the interpretation of trial results and subsequently, implementation decisions.

The Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) guidelines recommend that trials should plan and implement robust processes for monitoring adherence and describe these in the protocol [3]. This may include the measurement of adherence and how this will be collected, whether there is a defined acceptable minimum adherence level, and a rationale for these decisions.

However, defining and quantifying intervention adherence within the context of individual trials can be challenging. Within pharmacological trials, there are standardised published guidelines to enhance the

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quality of measuring and reporting adherence [4], e.g. the Medication Adherence Reporting Guideline (EMERGE) [5]. However, the same cannot be said for non-pharmacological interventions. There are multiple, and sometimes conflicting definitions of the term 'adherence' within the literature but one of the more widely used is the WHO [6] definition of "the extent to which a person's behaviour – taking medication, following a diet, and/or executing lifestyle changes with agreed recommendations from a health care provider". The Consolidated Standards of Reporting Trials (CONSORT) statement, Consensus on Exercise Reporting Template (CERT) and Template for Intervention Description and Replication (TIDieR) checklists outline the need for RCTs of non-pharmacological treatments to report detailed information about the intervention including adherence both at participant and care provider levels [7–9]. Whilst it is not uncommon to see the concept of adherence integrated into the reporting of RCTs, it appears the measures of adherence are highly variable and that there is no consensus on best practice. A recent review demonstrated that, particularly in trials of complex interventions, measurements of adherence were highly variable in both quality and content [10]. The literature is plagued with inconsistencies in the terminology used and varied definitions of adherence [11], e.g. use of the terms compliance, fidelity, engagement, etc., each with slightly differing connotations.

Current literature recommends that a sensitivity statistical analysis should be performed for RCTs, in addition to intention to treat (ITT), which aims to estimate the treatment effect among participants considered to have good intervention adherence, especially in the presence of a high rate of treatment non-adherence [12]. For example, a per-protocol analysis (only including participants that have not deviated from the protocol); however, this reduces the sample size, and hence power, of the analysis and can introduce selection bias if the remaining participants are no longer balanced across the groups. Similar concerns can arise from an as-treated (or *on-treatment*) analysis, in which the participants are analysed according to the treatment [13]. Therefore, outcomes derived from per-protocol and on-treatment analyses should be interpreted with care.

Complier average causal effect (CACE) analysis is less likely to provide a biased estimate of the potential intervention effect as it is randomisation-respecting [14]. CACE analysis provides estimates by comparing participants of the intervention group who adhered to the treatment with participants of the control group who would have adhered to the treatment had it been offered.

No matter the method used, in order to understand the results, it is fundamental that intervention adherence is well defined and reported. This review aims to describe current practice related to the definition, measurement, and reporting of adherence in non-pharmacological RCTs, and how this information is incorporated into the analysis and interpretation of trial results.

2. Methods

2.1. Searches

We searched all phase III RCTs published between 1st January 2018 and 30th June 2020 in the National Institute for Health Research (NIHR) Journal Library database for the Health Technology Assessment (HTA), Programme Grants for Applied Research (PGfAR), and Public Health Research (PHR) funding streams. We focussed on the NIHR as they are the UK's largest funder of health and care research. Our review focused on the peer-reviewed reports that are a requirement upon completion of the grant [15]. We chose to focus on the reports published in the NIHR journals library, rather than journal articles, given the comprehensive methodological information that is provided. We felt the details required regarding the measurement and statistical handling of adherence, were more likely to be located in the reports. All reports are written in English, and no search terms were needed as a manual search of all published reports, within our defined period, was feasible given the size of the database. The time interval (2.5 years) was considered adequate to capture current practice in trials of health interventions.

2.2. Study inclusion and exclusion criteria

RCTs were included if they used individual or cluster randomisation, with no restrictions on the number of trial arms or on trial populations. We included both superiority and non-inferiority trials, either with a parallel-group or a cross-over design, in which the intervention under observation could be of any type but not an Investigational Medicinal Product (IMP). We excluded all clinical trials of IMPs, typically phase IV, by screening the reports against the Medicines and Healthcare products Regulatory Agency algorithm and/or by searching on the European Union Drug Regulating Authorities Clinical Trials (EudraCT) Database number. Trials solely reporting on the economic evaluation of an intervention were also excluded, as well as follow-up studies of an RCT. Two authors screened all reports' titles and abstracts against the inclusion and exclusion criteria with any disagreements resolved by a third author.

2.3. Study quality assessment

Formal assessment of study quality is important in systematic reviews seeking to determine the effectiveness of an intervention, but this review sought to describe current practice regarding adherence in clinical trials with heterogeneous interventions. As such we did not assess trial quality as this would not impact our findings or their interpretation.

2.4. Data extraction strategy

One author extracted data, using a piloted Microsoft Excel extraction sheet, information on study characteristics (subject area, study design, setting, description of the intervention, number of participants randomised, primary outcome measures), statistical analyses and results (primary analysis, and other analysis when used) for all the included studies. All included reports were then reviewed by a second author who checked extracted data for accuracy and completeness with disagreements resolved through consensus with a third author. Data were also collected regarding intervention adherence and rationale, terminology used, how this was measured, and whether it was considered when analysing and interpreting the results. Subject areas were subjectively defined based on the primary nature of the intervention from: behaviour change, surgical, non-investigational medical device, physiotherapy/rehabilitation, psychological change, or other (training/monitoring/educational) (Table 1).

2.5. Data synthesis and presentation

Included reports were highly heterogeneous in respect to population, intervention and setting and therefore a narrative summary was

Table 1
Definitions of intervention categories.

Intervention category	Definition
Behaviour Change	An intervention that aims to shift behaviours in order to prevent illness onset/worsening
Medical Device	An intervention that includes a non-investigational medical device
Physiotherapy/ rehabilitation	An intervention where the main focus is on physical exercise, movement, or physical activity
Psychological Therapy	An intervention consisting of talking therapies aimed at treating a mental health problem
Surgical	An intervention that includes a surgical procedure
Other	Any intervention that does not fit into the other categories including training, monitoring, education, and diagnostics.

performed to synthesise findings. Summary data are presented with raw numbers and associated percentages where appropriate.

3. Results

The search of the NIHR Journals (HTA, PGfAR and PHR) for the period between 1st January 2018 and 30th June 2020, yielded a total of 237 reports that were potentially eligible for inclusion (HTA $n = 174$; PGfAR $n = 22$; PHR $n = 41$). The third review author was referred to 34 discrepancies out of 320 (10.6%). Seventy-six (32.1%) reports met all the eligibility criteria and were included in this review. In all, 161 studies were excluded: 140 based on title information, 19 on abstract information and two following full text review. The PRISMA flow chart depicting through the review is shown in Fig. 1.

3.1. Characteristics of the included studies

A summary of studies included are presented in Supplementary Table 1. Of the 76 reports, interventions categorised as behaviour change ($n = 23$, 30.3%) were evaluated most frequently, followed by surgical interventions ($n = 13$, 17.1%) and physiotherapy/rehabilitation ($n = 12$, 15.8%). Most studies ($n = 74$, 97.4%) were UK-based, while two (2.6%) were conducted in the Republic of Ireland [16,17]. The setting varied among the 76 included trials; most were hospital based ($n = 25$, 32.9%). Fifty-eight (76.3%) were individually randomised RCTs and 18 (23.7%) were cluster RCTs.

3.2. Adherence reporting

Among the 76 studies in the review, eight (10.5%) did not report measurements of adherence. Of those eight, five [18–22] included an evaluation of intervention fidelity which focused on how well the intervention was delivered rather than the extent to which it was received by the participants, two [23,24] were only related to a pharmacological element of the intervention (e.g. medication consumption) and to date one [25] had not reported findings. These studies were excluded from subsequent analysis.

3.3. Measurement of adherence

Of the 68 reports that assessed adherence, 49 (72.1%) undertook analysis to adjust for adherence and an additional 19 (27.9%) assessed adherence but did not undertake analysis (Table 2). Eight (11.8%) used the term 'adherence' only, 11 (16.2%) used only 'compliance', and 49 (72%) used another term (attendance, receipt of intervention, engagement, responsiveness, crossover, concordance, etc) or a combination of terms.

Measures of adherence included (Fig. 2): session attendance ($n = 27$,

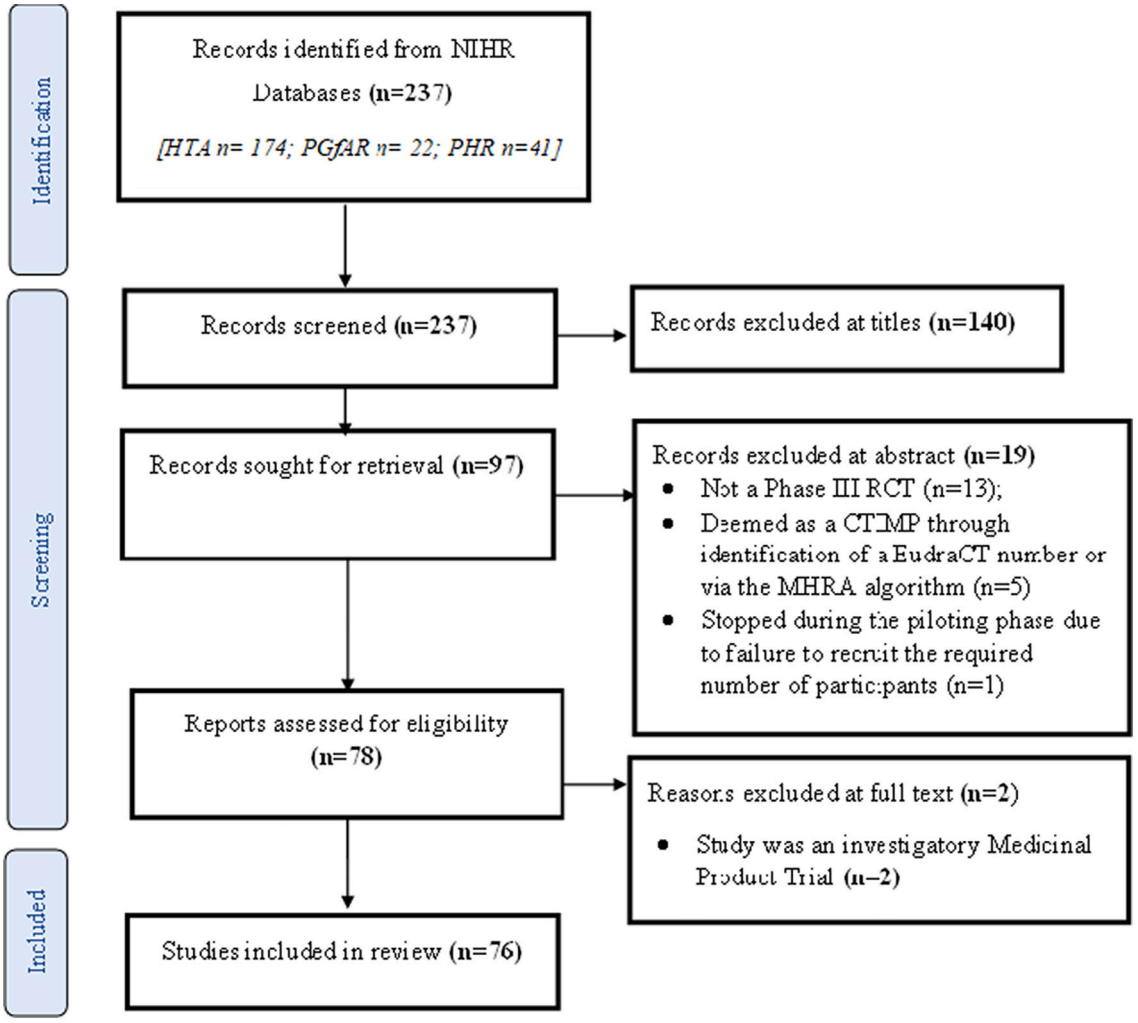

Fig. 1. PRISMA flow diagram of literature search and study selection phases; n, number. NIHR, National Institute for Health Research; HTA, Health Technology Assessment; PGfAR, Programme Grants for Applied Research; PHR, Public Health Research; CTIMP, Clinical Trials of Investigational Medicinal Products; EudraCT, European Union Drug Regulating Authorities Clinical Trials Database; MHRA, Medicines and Healthcare products Regulatory Agency.

Table 2
Terminology used and measures of adherence, including analysis to adjust for adherence, in trials that reported on intervention adherence.

Author (year)	Terminology	Parameter (or domain) used to measure adherence, and/or defined minimum acceptable level of adherence	Rationale for adherence threshold	Adherence analysis	Analysis type
Behaviour Change					
Adab et al. (2018) [26]	Adherence	Adherence, exposure, participant responsiveness and quality (of delivery)	Did not perform analysis		
Bonell et al. (2019) [27]	Compliance and adherence not used in respect of the receipt of the intervention	Exclusion of control schools that implemented elements of the intervention	n.a	Yes	PP
Crombie et al. (2018) [28]	Engagement	Number of participants responding to SMS	Did not perform analysis		
Daley et al. (2019) [29]	Adherence	Session attendance and continuing to follow the program through assessment of participants' adherence to daily self-weighing	n.a	Yes	Other
Deluca et al. (2020) [30]	Adherence	Monitoring remotely when the smartphone device is connected to the internet or when the web application is accessed	n.a	Yes	Other
Everitt et al. (2019) [31]	Compliance/adherence	Sessions completed (Web-based: at least 4 web-based and one or more telephone support calls; telephone-delivered: at least 4 telephone)	None	Yes	CACE
Ford et al. (2019) [32]	Compliance/adherence	Session attendance (all six sessions offered)	None	Yes	CACE
Gaughran et al. (2020) [33]	Compliance	Unclear	None	Yes	CACE
Giles et al. (2019) [34]	Extent of intervention received	Number of participants receiving the allocated intervention	Did not perform analysis		
Hajek et al. (2019) [35]	Adherence/compliance	Excluding the abstainers using non allocated products (5 days or more)/ excluding participants who did not attend any session	None	Yes	PP
Harrington et al. (2019) [36]	Engagement	Inclusion of the schools who engaged with ≥70% of the programme	None	Yes	PP
Harris et al. (2018) [37]	Adherence	Session attendance by nurses	None	Yes	Other
Hewlett et al. (2019) [38]	Compliance to treatment/adherence to session plans. (The word 'compliance' is used here as a statistical term; clinically the word adherence is used to describe active rather than passive decisions to participate.)	Session attendance (at least 2, session 1 and any other session)	Yes "if individuals in the RAFT programme intervention arm were considered participants only if they attended the first session (which might then have an impact on their outcome), then the offer of the intervention does affect outcome. To address this issue, the two-stage least squares (2SLS) CACE estimation were carried out separately to allow for loss to follow-up that was dependent on compliance."	Yes	CACE
Holt et al. (2018) [39]	Attendance/compliance	Compliance as attendance of at least one foundation course.	None	Yes	CACE
Humphrey et al. (2018) [40]	Participant responsiveness and reach	Procedural fidelity, participant responsiveness and reach	n.a	Yes	Other
Hunter et al. (2019) [41]	Engagement	Recording of daily activity and web usage	Did not perform analysis		
Ismail et al. (2019) [42]	Adherence/compliance	Participants who attended at least one intervention session	None	Yes	PP
Madan et al. (2019) [43]	Adherence/compliance	Based on the possibility that participants are not adherent to the intervention (not having access to their behavioural change program)	n.a	Yes	PP
Murray et al. (2018) [44]	Compliance	'high usage' on a web-based self-management programme (usage ≥the median of 4 days). Excluding participants who were suspected to have been exposed to the alternative intervention	None	Yes	CACE/ Other
Osborn et al. (2019) [45]	Attendance/engagement	Number of sessions attended/setting goals	Did not perform analysis		
Peckham et al. (2019) [46]	Compliance	Compliance with the intervention depending on number of sessions attended	n.a	Yes	CACE
Viner et al. (2020) [47]	Compliance	Compliance with the program defined as attendance of the first session plus	None	Yes	CACE

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Table 2 (*continued*)

Author (year)	Terminology	Parameter (or domain) used to measure adherence, and/or defined minimum acceptable level of adherence	Rationale for adherence threshold	Adherence analysis	Analysis type
		five or more of the twelve sessions offered			
Wyatt et al. (2018) [48]	Compliers with the intervention are children receiving at least four sessions of drama and the one-to-one goal setting session	Number of sessions received by the children and parents; number of participants receiving the intervention as allocated	Did not perform analysis		
Medical device					
Brocklehurst et al. (2018) [17]	Compliance	Recording of the thumbprint entries on the Guardian system	Did not perform analysis		
Costa et al. (2018) [49]	Adherence	Excluding participants who did not receive the allocated intervention	n.a	Yes	PP
Costa et al. (2020) [50]	Compliance/adherence	Compliers defined as participants who wore their allocated treatment for a period of ≥6 weeks without any change in treatment during this period/CACE analysis with different thresholds (minimum of 4 weeks and minimum of 2 weeks treatment allocation)	None	Yes	CACE
Kapoor et al. (2019) [51]	Adherence/compliance with device usage	Excluding participants who did not receive a device	n.a	Yes	PP
Nixon et al. (2019) [52]	Compliance/adherence	Excluding participants who did not achieve at least 60% compliance with their allocated mattress prior to developing a pressure ulcer of category ≥2, or the end of the treatment phase, whichever occurred sooner (other reasons apply)	None	Yes	PP
Perkins et al. (2019) [46]	Compliance/adherence	Compliance was defined as whether or not a participant received their allocated intervention up to the point of death, liberation, reintubation or tracheostomy (whichever came first). Excluding participants who had violated the protocol (did not receive the intervention as allocated)	n.a	Yes	PP
Physiotherapy/rehabilitation					
Ashburn et al. (2019) [53]	Compliance	Session attendance (excluding those who received less than 7 sessions) and repeat failing to complete >50% diary days	None	Yes	PP
Barker et al. (2019) [54]	Compliance/adherence	Session attendance (4 – partial, 7 – full attendance)	None	Yes	CACE
Clare et al. (2019) [55]	Compliance/adherence	Session attendance (at least 10, maximum 14 sessions)	None	Yes	Other
das Nair et al. (2019) [56]	Adherence/compliance	Session attendance (at least 4)	Yes, based on their previous studies that people would find some benefit from attending at least four sessions	Yes	CACE
Hay et al. (2018) [57]	Adherence	People who had received exercise intervention in line with protocol/self-reported exercise adherence	n.a	Yes	PP/Other
Lamb et al. (2018) [58]	Compliance to session attendance/ adherence to exercise intervention (to treatment)	Session attendance (>75% of scheduled sessions)	None	Yes	CACE
Lincoln et al. (2020) [59]	Adherent/compliance	Cognitive session attendance (at least 3)	None	Yes	CACE
McClurg et al. (2018) [60]	Adherence/compliance	The number of times the bowel massage was done per week recorded in a diary and self-reported changes in lifestyle (diet and exercise)	Did not perform analysis		
Palmer et al. (2020) [61]	Adherence	Adherers to key components of the intervention (recommended practice and support, or puzzle book received). A minimum of six puzzle books and four contacts was used as a measure of adherence to the intervention.	None	Yes	PP
Ridsdale et al. (2018) [62]	Adherence/compliance	Compliers are those attending all sessions (i.e. received full treatment), which is 4 in the intervention group	None	Yes	CACE
Shaw et al. (2020) [63]		Attendance to the therapy, liaison with employment contact, practice activity	Did not perform analysis		

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Table 2 (*continued*)

Author (year)	Terminology	Parameter (or domain) used to measure adherence, and/or defined minimum acceptable level of adherence	Rationale for adherence threshold	Adherence analysis	Analysis type
	Fidelity around delivery and implementation (patient actions were also considered)	and exercise, lifestyle change, arranged activity, liaise with professionals			
Surr et al. (2020) [64]			Compliance/adherence	Compliers defined as care homes who would have received at least one cycle of Dementia Care Mapping to an acceptable level (all components of the cycle completed) had it been offered to them	None
Yes	CACE				
Psychological Therapy					
Cottrell et al. (2018) [65]	Adherence	Received at least 1 session of the allocated treatment. Excluding protocol violators.	None	Yes	CACE and PP
Jahoda et al. (2018) [66]	Adherence	Excluding participants who did not attend 8 Beatit (manualised behavioural activation) therapy sessions or 6 StepUp (adapted guided self-help) sessions	None	Yes	PP
Johnson et al. (2019) [67]	Attendance/engagement	Psychoeducation session attendance	n.a	Yes	Other
Jones et al. (2018) [68]	Attendance	Number of attendances at the groups meeting	Did not perform analysis		
Morrison et al. (2019) [69]	Compliance	Session attendance (at least 6)	None	Yes	CACE
Serfaty et al. (2019) [70]	Compliance	The measure of compliance was the number of CBT sessions attended before the latest follow-up (18 or 24 weeks) for which the individual had outcome data. Compliers were defined as those who had at least one session of CBT.	None	Yes	CAITT
Surgical					
Beard et al. (2020) [71]	Compliance	Whether the operation was delivered as intended or changed (e.g., partial to total knee replacement)	n.a	Yes	CACE
Bhatnagar et al. (2020) [72]	Adherence	Recording of number of participants receiving the allocated intervention	Did not perform analysis		
Cooper et al. (2019) [73]	Compliance and adherence not used in respect of the receipt of the intervention	Whether they received the allocated treatment (LASH or EA intervention)	n.a	Yes	PP
Costa et al. (2018) [74]	Crossover	Whether they received the allocated treatment (locking plate or intramedullary)	n.a	Yes	PP
Gohel et al. (2019) [75]	Concordance with the treatment (compression therapy)/Non-adherent	Protocol deviators	n.a	Yes	PP
Hemming et al. (2020) [76]	Compliance	Included women who followed the protocol and received the treatment as allocated	n.a	Yes	PP
Jayne et al. (2019) [77]	Adherence/compliance	Excluding participants who did not have surgery and classing them with respect to the first intervention they received	n.a	Yes	PP
Khan et al. (2018) [78]	Compliance/Adherence	Recording of number of participants receiving their allocated treatment (assessment of erroneous return of cell-salvaged blood in the control group)	Did not perform analysis		

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Table 2 (*continued*)

Author (year)	Terminology	Parameter (or domain) used to measure adherence, and/or defined minimum acceptable level of adherence	Rationale for adherence threshold	Adherence analysis	Analysis type
Maguire et al. (2020) [79]	Compliance	Excluding participants with treatment deviations on >20% of visits	None	Yes	PP
Mallucci et al. (2020) [16]	Compliance/Adherence	Recording of the number of participants receiving the allocated intervention	Did not perform analysis		
Markus et al. (2019) [80]	Treatment Allocation	Including participants who received the assigned treatment and had at least 50% vertebral artery stenosis confirmed by angiography	n.a	Yes	PP
Sharples et al. (2018) [81]	Compliance	Compliers are those whom the surgery was completed as planned	n.a	Yes	CACE
Ulug et al. (2018) [82]	Compliance/adherence	Adherer defined as participants who were randomised to intervention strategy, subsequently found not anatomically suitable, undergoing open repair. Failure to receive the allocated treatment for any other reason was classified as non-adherence	n.a	Yes	CACE
Others (training/monitoring/diagnostic and others)					
Andrews et al. (2018) [83]	Compliance	Completed the study without protocol violation and complied with administered treatment	n.a	Yes	PP
Francis et al. (2020) [84]	Adherence/concordant	Non-compliers as participants who have departures from randomised treatment	n.a	Yes	CACE
Foy et al. (2020) [85]	Receipt of the intervention	Receipt of education outreach meeting/ joining rate/outreach support/s outreach meeting/reports received as intended (allocated)	Did not perform analysis		
Gulliford et al. (2019) [86]	Use of the decision support tool by the general practitioner	Session attendance (all sessions i.e. 4 in intervention)	Did not perform analysis		
Haighton et al. (2019) [87]	Reach of the intervention	Number of participants receiving the allocated intervention	Did not perform analysis		
Lovell et al. (2019) [88]	Fidelity of the training	Number of training sessions attended by the staff	Did not perform analysis		
Selby et al. (2018) [89]	Compliance with visits attendance/ compliance with the Enhanced Liver Fibrosis test/Compliance with cirrhosis management/Adherence in the context of treatment implementation	No full results available yet (number of visits attended in time for compliance, type of tests and number of tests done in time for compliance)	Did not perform analysis		
Wykes et al. (2018) [90]	Perception	Number of ward activities/number of participants in the session	Did not perform analysis		

CACE, Complier average Casual Effect; PP, Per-Protocol, CAITT, Contamination-adjusted Intention to treat; CBT, Cognitive Behavioural Therapy; n.a, Not Applicable; DCM, Dementia Care Mapping; LASH, Laparoscopic Supracervical Hysterectomy; EA, Endometrial Ablation; SMS, Standard Messaging Service.

41.2%), whether participants received their allocated intervention/ treatment (n = 27, 41.2%), self-reported (diaries, questionnaires, SMS responders) ($n = 8$, 11.8%) and five (7.3%) used mixed methods e.g. two or more of the methods mentioned. One study did not provide a description of how adherence was measured. Behavioural change (n = 10, 43.5%), psychological therapy (n = 5, 83.3%) and physiotherapy/ rehabilitation (n = 8, 66.7%) interventions predominantly based their measurements on recording the number of sessions attended. Whereas, medical device (n = 4, 66.7%) and surgical (n = 13, 100%) trials primarily recorded the number of participants receiving the allocated intervention. A rationale for applying an intervention threshold was only provided in two (4.1%) of the 49 reports. The reasoning was based on (1) previous findings by the authors who stated 'people would find benefit from attending at least four sessions' [56] and (2) that 'if individuals in the RAFT programme intervention arm were considered participants only if they attended the first cognitive-behavioural session (which might then have an impact on their outcome), then the offer of the intervention does affect the outcome' [38].

3.4. Incorporation of adherence in trial findings

Seventy three (96.1%) studies analysed their primary outcome on an intention to treat basis (ITT), one (1.3%) on a complete-case analysis and two (2.6%) were not clearly stated. Forty-nine (72.1%) of the 68 reports that measured adherence performed an additional statistical analysis to attempt to quantify the possible impact of adherence on the primary outcome (Supplementary Table 2). Nearly half (n = 22, 44.9%) used CACE, or the similar Contamination-adjusted Intention to treat (CAITT), 22 (44.9%) performed per-protocol (PP) analysis and other analysis e.g. sensitivity analysis were used in 9 (18.4%) reports, 3 [6.1%] performed multiple types of analyses.

Studies reported adherence rates ranging from just 39% to 98.9% (mean 80.8%; median 85.6%) (Supplementary Table 2). Higher rates were seen in those that measured adherence by intervention allocation such as surgical and medical device trials, whilst lower rates were identified in session attendance in trials of behavioural change, and psychological therapy interventions. Although the majority of trials (n = 33, 67.3%) did not show a difference in findings after conducting a sensitivity analysis for adherence rates, a third of trials did The majority of authors considered this a dose-response effect as these were mostly measured based on the number of sessions attended. For eleven trials (22.4%) the interpretation of results differed when including adherence data in their statistical models for primary or secondary outcome data.

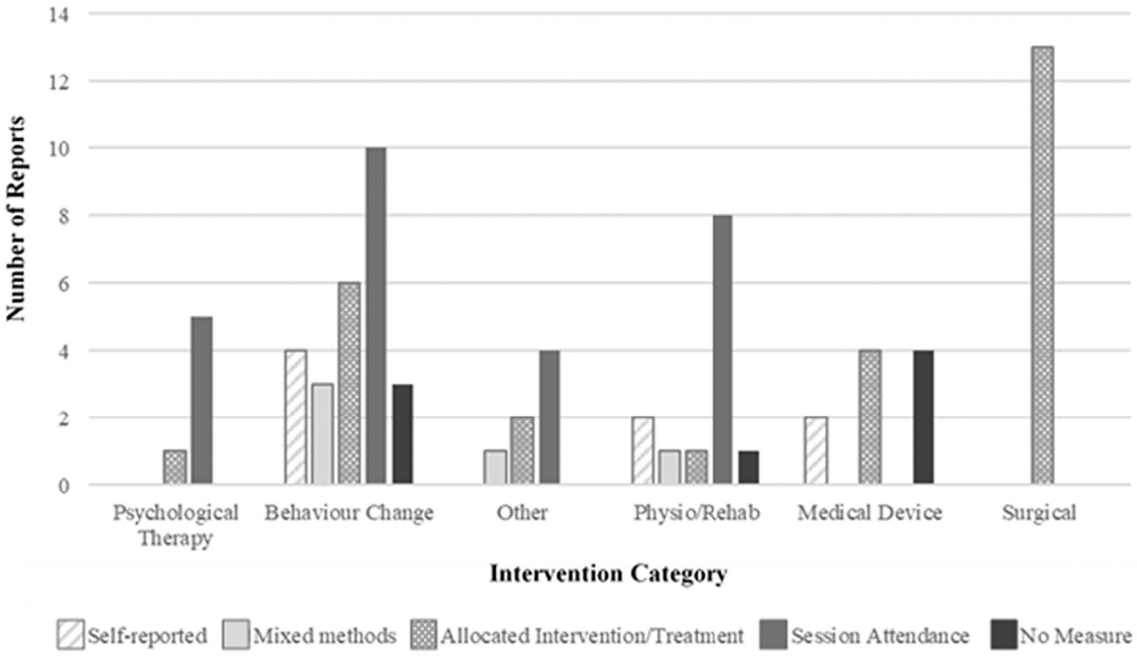

Fig. 2. Adherence measures employed by reports according to intervention category.

4. Discussion

Adherence is a key determinant of health outcomes and an important concept in the analysis and interpretation of randomised trials: appropriate consideration of adherence is now widely recommended [7,8,91]. In order to understand results from trials and inform clinical practice, it is fundamental that treatment adherence is consistently defined, considered in sensitivity analyses, and reported, but our results suggest that current practice is inconsistent. We found that although the vast majority of studies reported adherence, terminology around adherence and compliance varied widely, and over a quarter of studies did not report any analysis of adherence data. Measurement of adherence also varied greatly between clinical areas with surgical and medical device trials largely concerned with whether participants received the allocated intervention, whereas trials of rehabilitation, behavioural change, and psychological interventions were primarily concerned with session attendance. How adherence is defined, measured, and incorporated clearly matters because over a third of studies report a difference in findings between the primary and sensitivity analyses. This will have important implications for clinical practice.

The challenges in measuring and incorporating adherence within analyses are increasingly recognised [10,92] but an essential starting point for greater consistency would be the terminology used. We found variation between and even within studies, particularly in the conflation of adherence, compliance, and fidelity. Reducing this variation is an important first step and requires a common understanding of the terms between areas of clinical practice and members of the clinical research team. In a biopsychosocial model of care, the term adherence is more appropriate as it respects the patient's autonomy, yet the most widely used statistical technique to account for adherence is CACE, therefore is likely to increase the use of the less preferred term compliance [6,12].

Central to the WHO definition of adherence is that it is a behaviour from the patient rather than clinician [6]. Conceptually, this is perhaps clearest in rehabilitation interventions where the patient will determine whether they follow a prescribed exercise programme. Fidelity, on the other hand focusses on how well the trial follows the randomisation and protocol, for example whether the clinician prescribes/delivers the correct intervention [93,94]. This dichotomy is perhaps oversimplistic as it does not fully capture the complexity of these behaviours and increasingly shared nature of decision making in healthcare. The balance of these two elements will also vary in different clinical situations (e.g. patients may have little say in the exact model of clinical implant used in an operation, but they will have a far greater say in whether they perform a home exercise programme).

Complex interventions and packages of care perhaps present particular challenges and raise many questions [10,95]. For example, when a relatively simple intervention is considered, such as a medication, measurement of adherence should focus on whether the participant took the medication. In contrast a programme of exercises may contain a series of weekly clinic visits, and multiple exercises performed at home each day. What should be measured in this instance? Performance of each exercise, whether a session was conducted each day, whether the patient attended the clinical session, or a combination of these elements? The situation becomes even more complex if the intervention consists of a surgical procedure and rehabilitation programme. The vast majority of rehabilitation studies in our review defined adherence as attendance at the clinic sessions but it is unclear whether this adequately reflects the total volume of exercise performed and physiological effects. Clearly any measurement must be feasible and be cognisant of the burden on participants and clinicians, but our review raises questions about whether greater emphasis should be placed on measuring what matters, rather than what is easy to measure. Equally, more attention could be paid to the relationship between how adherence is defined in a particular study and the logic model pertaining to the potential mechanism of action. Researchers could make more attempts to justify how 'adherence' was defined and consider sensitivity analyses around such definitions.

Advances in technology, such as temperature sensors and wearable activity trackers, are starting to provide potentially more objective measures for some clinical scenarios such as orthoses [96] and exercises [97] but this is unlikely to be an option in all areas of clinical practice. Elsewhere, study-specific subjective measures, such as questionnaires and diaries, have been developed but few of these are validated or used more than once which limits the comparability of study results and prohibits pooling of data in meta-analyses [10,92]. Attempts have previously been made to improve the reporting of adherence in particular clinical disciplines such as substance abuse and health behaviour change and non-pharmacological disciplines such as exercise and physical

activity interventions, but the situation remains unsatisfactory [10,94,98–101]. There is still a lack of uniform/transferable guidance, or framework for ensuring comprehensive measurement, analysis, and reporting of adherence. It also remains unclear how thresholds for adherence are determined within research into non-pharmacological therapies. For example, we often see acceptable adherence defined as a specific figure such as 80%, but how often is this based on a sound theoretical framework? In our review, only two reports provided a rationale for the adherence threshold they used. Further methodological work and guidance is urgently needed in this area. Funding bodies must work with researchers to develop evidence-based adherence thresholds which can then be applied in future clinical trials.

Our review is novel in that, to our knowledge, it is the first systematic review to consider recent practice across the spectrum of clinical research within a country. Instead of reviewing published papers, we searched for final reports from the NIHR library. This confers two principle benefits: the NIHR is the largest funder of clinical research within the UK, funding and project delivery is subject to extensive peer-review and expert scrutiny, so is likely to reflect contemporary high-quality research practice; and these reports are typically around 200 pages in length so contain much greater methodological detail than can be reported in journal publications. The primary limitation is that this work is that the research does not reflect international research practice and, therefore, we must be cautious not to generalise these findings beyond the UK. Secondly, although the length of the reports allows additional detail to be reported it is also conceivable that we missed some information. We attempted to mitigate against this through use of a second reviewer to check for accuracy and completeness and using a third reviewer to resolve any disagreement.

We chose to include phase III clinical studies across a range of clinical areas to capture current practice in a range of clinical specialities and disciplines. Given the additional complexity of phase IV trials and the predominance of pharmacological interventions and long term implementation studies, we chose not to include them in our review as this would further increase the heterogeneity of our sample. Inclusion of a wider range of study designs should be considered for future research.

Lastly, given the absence of a universal classification system that we could apply to the range of interventions being tested in the RCTs we identified, we developed our own subjective classifications e.g. behaviour change, psychological etc. Although attempts were made to capture the main emphasis of the intervention in our classification process, this method is likely to have resulted in some misclassification as some interventions would include elements from more than one category. If future research is to continue to compare research practice, more thought should be given to a repeatable classification system.

5. Conclusion

Our findings indicate that although the majority of clinical studies report elements of adherence there is a lack of consistency in use of key terminology, and no systematic approach to its measurement, analyses, interpretation, or reporting. Given the importance of adherence within clinical trials, we consider that further methodological research, and a framework or guidance, should be developed as a matter of urgency.

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Author contributions

MB, JA, and CF conceived the study. AG, KJ, and RMC conducted the literature searches, screened eligible manuscripts and conducted the data extraction. MB, JA and CF acted as a third reviewer to provide consensus where required. MB, JA, KJ, and AG drafted the manuscript which all authors reviewed. All authors read and approved the final manuscript.

Availability of data and materials

All data generated or analysed during this study are included in this published article and its supplementary material.

Declaration of Competing Interest

The authors declare they have no competing interests.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.cct.2022.106788.

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