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Adverse event recording failed to reflect potential harms: a review of trial protocols of behavioral, lifestyle and psychological therapy interventions

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Abstract

Objective: To explore how potential harms are assessed in trials of behavioral, lifestyle and psychological therapy interventions.

Study design and setting: This study was a review of protocols from the National Institute of Health Research Health Technology Assessment and Public Health Research programmes. Protocols were included if the study was a randomized controlled trial and the intervention intended to change lifestyle or behavior to improve health or improve psychological outcomes.

Results: 95 of 151 protocols planned to record adverse events (AEs). Definitions of AEs were often not given and varied widely. Serious AEs were mostly defined using standards originally devised for pharmacological trials. Twenty-two protocols listed expected AEs. Few protocols described assessment of causation between AEs and intervention. Examples of useful AE recording practice were identified.

Conclusion: Monitoring and recording AEs in behavioral intervention trials was variable and frequently based on reporting guidelines for pharmacological trials. This may mean potential harms are being missed. Future trials should consider: 1) Potential harms posed by the intervention 2) How to define serious AEs 3) What are expected AEs. Further research to achieve consensus on AE recording is required, including identification of core adverse outcomes in clinical areas or caused by interventions.

Keywords: Adverse events; Harms; Randomized controlled trials; Public health; Psychological therapies; Behavioral interventions

1. Introduction

Non-pharmacological interventions can cause harm or unintended effects, yet within public health and psychological therapy fields, clinical trials have not adequately considered these outcomes [1–7]. This is of concern since intervention assessment in clinical trials requires risk-benefit analysis. Beneficial effects must be considered alongside harmful effects. This could leave harms, typically termed Adverse Events (AEs), unidentified.

Non-pharmacological interventions include social and behavioral interventions, psychological therapies and lifestyle interventions. There are examples where these interventions have caused unintended harm. A behavioral and social intervention called the 'Young People's Development Programme' aimed to decrease teenage pregnancy. In fact, it had the paradoxical effect of increasing pregnancy rates [8]. Social and emotional learning (SEL) interventions in schools have resulted in negative labelling, stigmatization, and peer to peer knowledge exchange [9]. Despite these harms being well documented in the literature, some SEL intervention trials have not considered or recorded these potentially harmful effects [9]. The lack of recording may suggest harms are not considered important in non-pharmacological studies. Furthermore, reliance on guidelines originally designed for pharmacological trials may result in attempts to measure harms failing or being overly complicated.

1.1. Reporting guidelines for harms within clinical trials

The International Conference on Harmonisation (ICH) Guideline on Good Clinical Practice (GCP) [10] sets down the core principles all clinical trials must adhere to. The ICH GCP definition for AEs devised for pharmacological trials is:

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What is new?

- Harms or unintended consequences are known to be possible from trials of behavioral, lifestyle and psychological therapy interventions, yet are not always appropriately or consistently evaluated in trials.
- Reliance on definitions for harms (typically termed adverse events) originally devised for pharmacological trials, may result in omission of important harms.
- The level of risk or likelihood of harm from an intervention should always be assessed in trials of these interventions.
- Better details on adverse event recording in protocols is needed to increase transparency and consistency and improve practice, but consensus is needed on the appropriate approach.
- Examples of useful AE recording practices identified from trials included in this review are discussed, for example: alternative definitions of what constitutes a serious adverse event or methods of deriving lists of expected adverse events.

"Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An adverse event (AE) can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product" [10].

For pharmacological and non-pharmacological trials, AEs defined as i) ***serious*** (Fig. 1) ii) can be attributed i.e. ***related*** to the intervention and iii) if unexpected must be reported within strict timelines to the Research Ethics Committee (REC). The rationale for this approach comes from pharmacological trials, in which a clinical vigilance model allows expedited reporting of such events so that dangerous trials can be quickly halted.

There are no other specific standards or guidelines for AE recording in non-pharmacological trials. The CONSORT trials harms extension [11] defines and specifies methods of assessment for the items on harms that should be recorded in clinical trials. The CONSORT Social and Psychological Interventions (SPI) extension [12,13] also notes that AEs should be defined and that the theory on the mechanism of the intervention may also inform potentially harmful effects [1]. It is unknown how behavioral change or psychological therapy trials are defining and assessing AEs. However, it has been noted that AE definitions and assessments are often modelled from ICH GCP which is not wholly applicable or useful in the context of these types of trials [3,14].

1.2. Aim and objectives

This review aims to identify how NIHR trial protocols evaluating behavioral, lifestyle and psychology therapy interventions planned to record potential harms.

The specific objectives are to determine:

- How AEs and serious[1] AEs are defined.
- If investigators list expected AEs in trial protocols.
- How investigators assess if an AE is caused by an intervention.
- If exclusions are made for AE recording and if these are justified.

[1] Serious AEs results in death, a life-threatening episode, an inpatient hospitalization or prolongation of hospitalization, persistent disability or incapacity, a congenital abnormality or any other medical event deemed significant by the investigator.

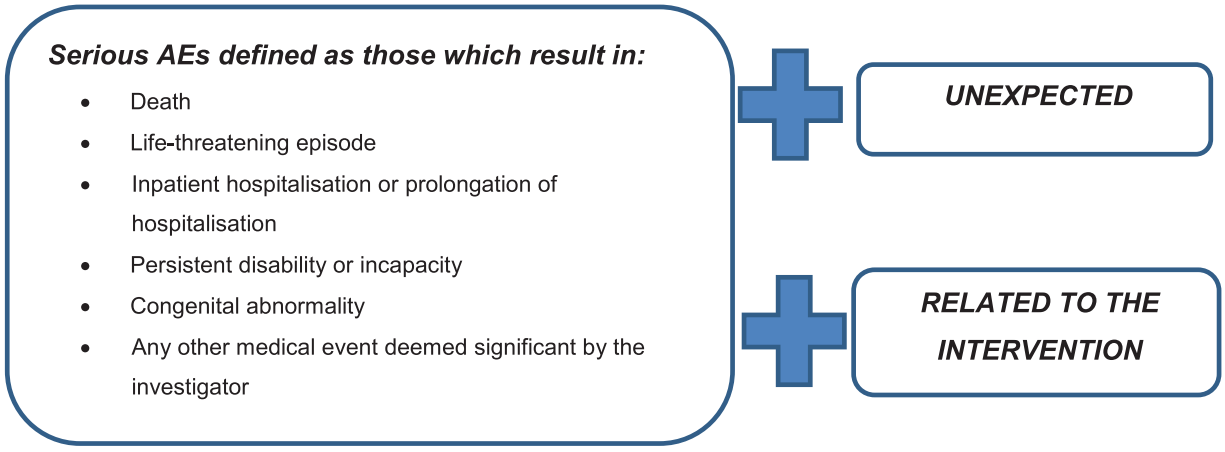

Fig. 1. Adverse events in non-pharmacological clinical trials which must be reported to the REC.

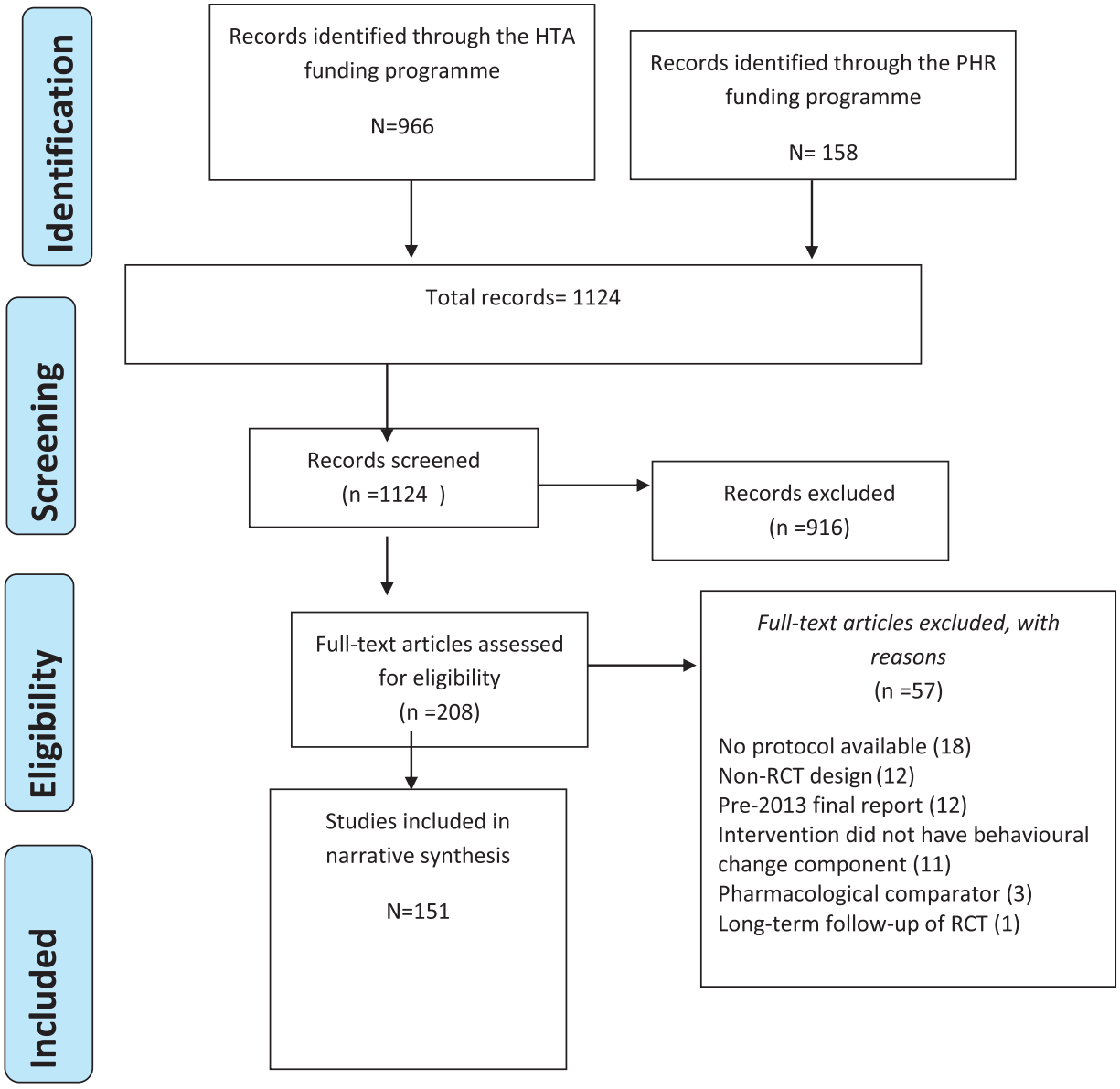

Fig. 2. Flow of protocols during identification.

2. Methods

The NIHR journals library site (https://www.journalslibrary.nihr.ac.uk/#/) was searched for all ongoing or completed NIHR-funded trials with an available protocol in June 2020. The search was restricted to "Primary Research" in the Health Technology Assessment (HTA) and Public Health Research (PHR) funding streams.

Projects must include a randomized controlled trial. Pilot and feasibility studies were included where there was an RCT component. Diagnostic and screening studies were excluded. Any population was included. Projects must include an intervention intended to change an individual's lifestyle or behavior to improve health, including all forms of psychological therapies. Projects where the comparator arm included a drug, medical procedure or device were excluded. Previous reviews undertaken on AE recording in NIHR trials [2,3] were completed in 2014. Therefore, this review excluded any projects which had finished and published a final report during or before 2013.

Titles and abstract, and if necessary, the full-text, were reviewed by DP to identify projects for inclusion in the review.

A standardized data extraction form was developed to record details from each protocol (see appendix A). Data was extracted by three reviewers (DP, CM, RG) using the latest version of the protocol. Ten percent of data extraction

Table 1. Clinical populations of included projects.

Clinical population	Freq (%)
Obesity and increasing physical activity	35 (23.2%) [19 in adults, 11 in children and 5 in adolescents]
Depression (all groups) and anxiety	19 (12.6%)
Other mental health conditions: Personality disorders [1], Schizophrenia [2], psychosis and bipolar disorder [2], self-harm [2], severe mental illness [4], OCD [1], psychiatric community patients(1) and anorexia [1]	14 (9.2%)
Sexual health/function	12 (7.9%) [5 in adults, 7 in adolescents]
Alcohol and substance abuse	12 (7.9%) [3 in adults, 9 in adolescents]
Smokers	8 (5.3%)
Primary school aged children-emotional wellbeing	7 (4.6%)
General mental health/wellbeing- includes refugees, NHS workers, schoolteachers, young offenders	5 (3.3%)
Autism/ASD	4 (2.6%)
Child behavior/parenting	4 (2.6%)
Dementia or Alzheimer's	4 (2.6%)
Carers (dementia, mental health)	3 (2%)
Looked after children/adolescents	3 (2%)
Learning disabilities	3 (2%)
Loneliness/older adult wellbeing	2 (1.3%)
Others (1 study each): Back pain, Tourette's, fear of falling, fatigue in rheumatoid arthritis, PTSD, oral health, IBS, CVD risk, breast feeding, MND, health care worker, bullying, musculoskeletal conditions, gamblers, IBS	16 (10.6%)
Total	151

records were checked independently. The findings were synthesized narratively to identify similarities and differences in approach.

3. Results

3.1. Protocols included

A total of 151 projects were identified as meeting the inclusion criteria; 71 from HTA and 80 from PHR. Fifty-seven projects were excluded because they did not provide a protocol (n = 18), were not an RCT design (n = 12), the project report was published before 2013 (n = 12), the intervention did not contain a behavioral change component (n = 11), contained a pharmacological comparator (n = 3) or was a long-term follow-up of an RCT (n = 1). Figure 2 shows the flow of protocols during protocol identification.

3.2. Protocol characteristics

Tables 1 and 2 categorize the population and interventions studied in included trials. The most common clinical groups were obese adults, adolescents or children (n = 35), depression and anxiety (n = 19) and other mental health populations (n = 14). Sexual health and alcohol/substance abuse were evaluated in 12 trials each. The most prevalent types of interventions were psychological therapies (n = 37), those aimed at increasing physical activity (n = 23) or making healthy lifestyle changes (n = 16).

Fifty-seven (38%) projects were an external pilot or feasibility study. The projects varied greatly in size, with sample sizes ranging between 40 and 6250 participants. Protocols were dated between June 2010 and May 2020.

3.3. Adverse events recorded

Ninety-five (63%) and eighty-nine (59%) of 151 protocols stated that non-serious and serious AEs would be recorded, respectively. This left a large number of protocols (27%; 36%) where it was not clear if non-serious or serious AEs would be recorded. A clear statement that AEs *would not* be recorded was given in 10% (n = 15/151) and 5% (7/151) of protocols, respectively. Justification for not recording non-serious AEs was given in 6/15 protocols, typically that the intervention was behavioral and not expected to cause harm (Figs. 3 and 4) [15–20].

Table 2. Interventions by type or type of behavior intended to change.

Intervention type or type of behavior being modified	Freq (%)
Psychological therapies	37 (24.5%)
Physical activity only	23 (15.2%)
Lifestyle- increasing activity and healthy eating	16 (10.6%)
Parenting programs and family therapies	14 (9.2%)
Alcohol or substance abuse behavior	12 (7.9%)
Sexual health including teenage pregnancy	11 (7.3%)
Social and/or emotional learning (includes emotional wellbeing)	9 (6.0%)
Smoking cessation	7 (4.6%)
Peer support or befriending	6 4.0%)
Other: data and relationship violence [2], social stories [2] gambling [1], back pain self-management [1], debt counselling [1], arts therapy [1], oral health behavior [1], returning to work [1], hand hygiene [1], motivational interviewing [1], anger management [1], standing up for myself (learning disability population) [1], loneliness and social networks [1], good behavior school [1]	16 (10.6%)
Total	151

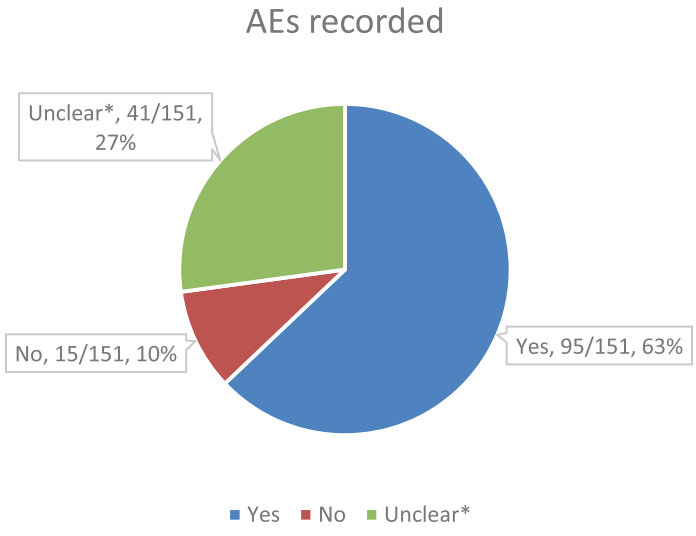

Fig. 3. Were AEs recorded?

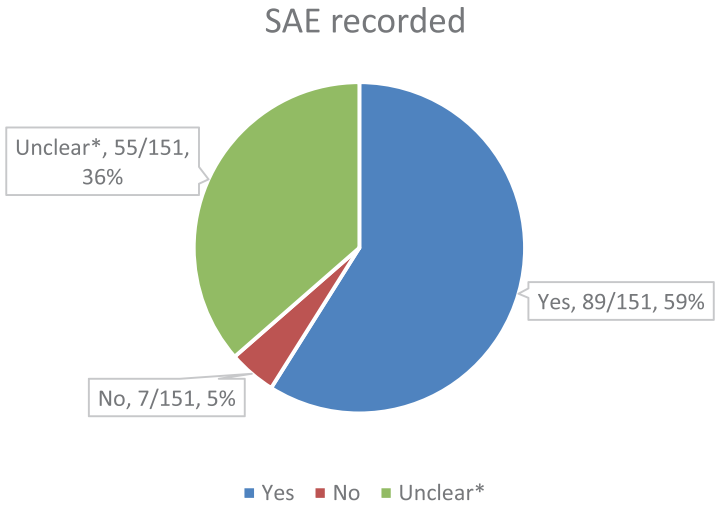

Fig. 4. Were SAEs recorded?
*Unclear denotes there was no mention in the protocol on AE recording.

Table 3. Protocols which excluded specific events as AEs.

Intervention	Population	Exclusions for AE recording + rationale
Behavioral activation therapy [37]	Depression in people who had a stroke	Further stroke related events were not classified as serious AEs, because these events were expected within this population.
Acceptance and commitment therapy [38]	Motor Neurone disease	All physical AEs (with the exception of self-harm) were excluded. (Note non-physical events that were to be considered AEs were specified in this protocol).
Cognitive-behavioral therapy [39]	Anxiety and depression for older victims of crime.	Physical illness and hospitalization were not recorded as AEs. These events were expected in this population (aged 65+ years) and were evaluated as unlikely to be related to the intervention.
Physical activity intervention [40]	Obese adults	Only events requiring medical attention that occurred during the intervention would be recorded as AEs.
Psychosocial intervention [41]	Asylum seekers and refugees	Stated it can be reasonably assumed that no physical AEs will be related to the intervention.

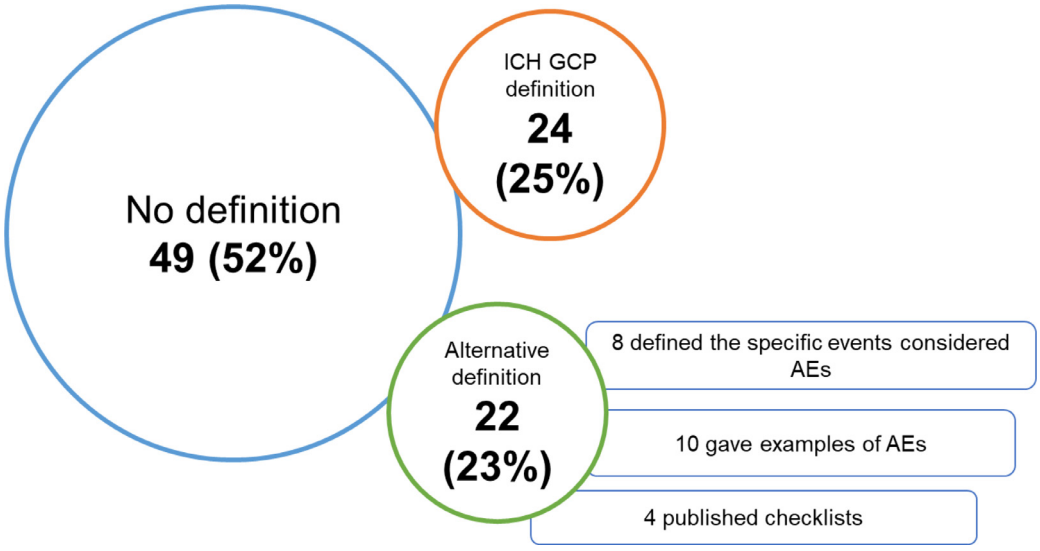

Fig. 5. Definitions of AEs.

3.4. Exemptions from AE recording

Twenty-five protocols made exemptions to AE recording. Eight of 15 protocols which stated non-serious AEs were *not* to be recorded **did** record serious AEs [18–25].

For SAEs, eight protocols restricted recording serious AEs to only those which were treatment-related [26–33] and four protocols restricted to unexpected and treatment-related SAEs [18,34–36]. Five protocols excluded specific events as AEs, see Table 3.

3.5. Qualitative research and harms

Six protocols explored harms or unintended consequences through qualitative research or a process evaluation but did not record event-level AEs [42–47]. Another eighteen protocols explored harms qualitatively, in addition to capturing event level AE data [26,31,35,48–62].

3.6. Definitions

Forty-nine of ninety-five protocols did not provide a definition for non-serious AEs. Twenty-two studies provided an alternative to the ICH GCP non-serious AE definition. Eight protocols defined the specific events considered as non-serious AEs [37–39,49,63–66]. Four protocols planned to use a dedicated and previously published checklist to record non-serious AEs or side effects of treatments [32,41,51,67]. Ten protocols gave examples of AEs [26,42,58,68–74] and only 18 protocols used the ICH GCP definition (Fig. 5).

For SAEs, the majority used the ICH GCP definition (n = 52) (Fig. 6). There were also examples of bespoke definitions (Table 4).

3.7. Causality/relatedness

Causality was assessed for protocols which stated they would record serious AEs (n = 89), and was poorly documented in the majority (Table 5). Most did not describe

Table 4. Examples of alternative definitions of SAEs.

Intervention	Serious adverse events*
Video-feedback intervention for children and foster carers to improve mental health outcomes of children with reactive attachment disorder [64]	Cases of death, hospitalization or maltreatment
Acceptance and commitment therapy in motor neurone disease [38]	ICH GCP definition plus new reports of suicidal ideation with active suicidal behavior/plans and imminent intent and reports of physical self-harm
Acceptance and Commitment Therapy for older people with treatment-resistant generalized anxiety disorder [57]	New reports of suicidal behavior during the ACT intervention
Lifestyle intervention (physical activity and healthy diet) to prevent obesity in primary school children	1. Unusual dieting behaviors 2. Unusual physical activity behaviors 3. Stigmatization of overweight/underweight children 4. Noticeable weight loss
Group arts therapy for diagnostically heterogeneous psychiatric community patients [65]	ICH GCP definition and SAEs for the purposes of this study may include: a) A participant making a suicide attempt b) A participant causing life threatening injury to another c) An event occurring during the course of the study which results in hospitalization or prolongation of existing hospitalization related to their mental health.
Return to work: peer support and CBT for common mental health disorders in NHS staff [60]	Self-harming or attempted or completed suicide by the participants or a serious or significant deterioration in a participant's mental state.
School-based intervention to prevent dating and relationship violence and address health inequalities among young people [54]	Any case of abuse that meets the criteria for "serious"
CBT for post-traumatic stress disorder [75]	ICH GCP definition plus in addition severe self-harm and harm to others.
Problem Adaptation Therapy For Individuals with Mild to Moderate Dementia and Depression [76]	ICH GCP definition plus new reports of suicidal behavior
Multi-component intervention (includes group therapy, one-to-one, improvement of knowledge, motivational interviewing) to reduce substance use and risk-behavior in adolescents engaged with the criminal justice system [77]	Defined as death, emergent substance use that requires referral for treatment by a specialist agency, raises safeguarding issues that require disclosure to third parties in accordance with the Addaction Safeguarding protocol, changes in the severity-offending pattern of concern to staff, any potentially iatrogenic effect of the intervention observed by, or reported to Interventionists, any event that is considered significant by research staff or principal investigator
Regular self-weighing to prevent weight regain after weight loss in obese adults [66]	Events related to bulimia, anorexia and self-harm or related to body dissatisfaction that result in hospitalization during the trial.
Sexual health promotion intervention for people with severe mental illness [78]	Self-harm, suicide attempt, violence to others or victim of violence
CBT for chronic symptoms of depression or anxiety in older victims of common crime [39]	ICH GCP definition plus any important medical event that may jeopardize the participant or may require an intervention to prevent one of the above characteristics/consequences.
Psychodynamic Interpersonal Therapy for women offenders who self-harm [52]	ICH GCP definition plus life threatening nature must take into account suicidal ideation e.g. suicide note
Psychosocial intervention for refugees [41]	ICH GCP definition plus suicidal ideation.

Table 5. Who assessed causality of an SAE?.

Who?	Freq. (%)
Central team i.e. trial manager, Chief Investigator, Trial management group	*33 (37%)*
Not described	31 (35%)
Joint approach: local trial team and central team discussion	18 (20%)
Independent trial committees: Trial Steering Committee or Independent Data Monitoring Committee	4 (5%)
Local trial team	3 (3%)
Total (Protocols which recorded SAEs)	89

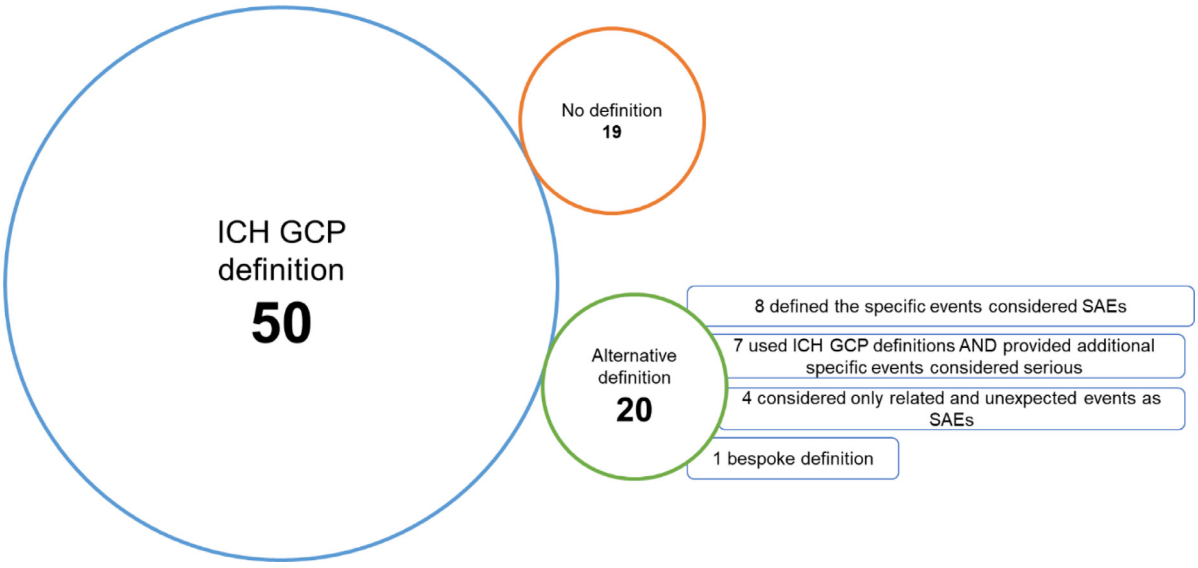

Fig. 6. Definitions of SAEs.

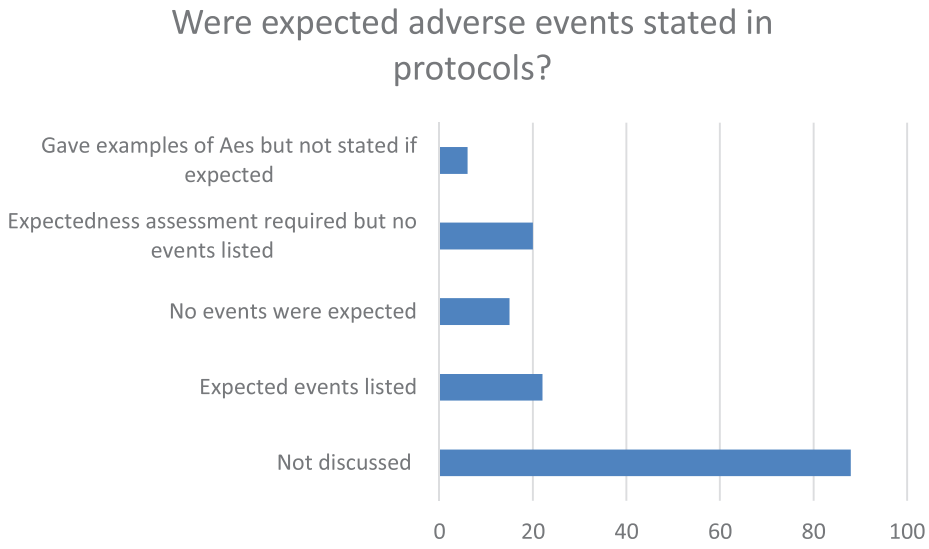

Fig. 7. Expected adverse events in protocols.

any details of causality assessment (n = 35) or noted it was required but did not give details of a rating scale (n = 28). The most common rating scale used was "Definitely related, probably related, possibly related, unlikely to be related or unrelated" (n = 26).

Most trial protocols indicated that the central team made causality assessment (N = 33) or a joint local trial investigators and central team approach (n = 18). Only two protocols acknowledged that causality assessment was difficult and stated, for example, '…that all SAEs will be forwarded to the Independent Data Monitor within 48 hours of the CI becoming aware of the event.' [78,79].

3.8. Expectedness

Only twenty-two protocols provided a list of expected events to which investigators could make their assessment of expectedness. However, only 4/22 protocols provided information about how the list was derived. One trial team [51] derived the list from events that had been recorded in previous, similar trials; two reviewed the literature for harms, [58,80] and one team consulted epidemiological data to estimate the expected number of deaths as a result of self-harm within the trial sample (Fig. 7) [81].

4. Discussion

This review of NIHR trial protocols evaluating behavioral, lifestyle and psychological interventions found ad-

verse events to be monitored with wide variability and lack of consistency. Assessing causality and expectedness is a key component of reporting requirements to UK RECs, and there was a lack of transparency on how AEs were assessed on these elements. AE definitions were often missing and varied even between trials of similar interventions. Serious AEs were frequently defined using the ICH GCP definition. Exemptions for AE recording mostly restricted recording to serious and/or related AEs.

A lack of consistency and transparency is perhaps not surprising given the absence of bespoke guidelines for AE recording in non-pharmacological trials and the reliance on guidance originally devised for pharmacological trials [3,14]. Pharmacological trials assess expectedness by referring to drug manufacturer documentation. For behavioral intervention trials, it is difficult to determine how *all possible* harmful effects could be listed a priori, with no comparable documents available. Only four protocols identified in this review described the methods they used to list expected AEs [51,58,80,81].

The absence of expected AEs in protocols may indicate investigators are struggling to adapt these standards. Theorizing the harmful effects of complex interventions for example by applying the process described in Bonnell et al's "dark logic models" [1] is recommended by the Consort SPI extension [12,13]. However, the complex causal pathways of unintended harms in behavioral interventions might mean investigators need more support on an individual trial level.

Determining whether individual AEs are caused by a behavioral intervention can be difficult, if not impossible in some cases [11,82]. It is unknown if there were difficulties in causality assessment since this was a review of protocols. Oquendo [82] found a lack of consistency in AE definitions, causality and assessment used across suicide prevention trials. Several protocols in this review described input from independent oversight committees on causality assessment, which may support investigators in these subjective assessments.

A further problem with using AE recording approaches modelled from pharmacological trials is the ICH GCP definition for serious AEs. This definition risks potentially important harms being missed particularly if investigators restrict recording to serious AEs (which this review found was often the case). There are unintended consequences of changing behavior which do not meet the ICH GCP category of seriousness. These include risk compensation; rebound effects and unsuccessful behavioral change programs leading to feelings of failure [83]. There were good examples where trial teams defined serious AEs outside the standard ICH GCP definitions (Table 4). Investigators need to consider defining serious AEs in this way in order to fully reflect the harms profile of an intervention.

Recording **all** AEs is time-consuming, particularly in populations with a high frequency of AEs. SAE reporting in an older adult trial of cranberry juice capsules was estimated to have taken 15 hours per week each for two research nurses, yet none of the SAEs recorded were considered related to the trial intervention or unexpected [84]. Similarly, a review of substance abuse clinical trials evaluating psychosocial interventions found all serious AEs were unrelated to the study interventions [85]. For efficiency, consideration should be given to exemptions in AE recording and not anchoring recording to ICH GCP definitions.

Qualitative sub-studies or process evaluations often included an objective to explore unintended consequences or harms. Indeed, the CONSORT SPI extension [12,13] discusses the importance of using the findings from qualitative studies to allow readers to weigh up an intervention's risks and benefits. Given the difficulty in determining all expected harms at the beginning of trials, qualitative methods can play an important role in identifying unexpected harms. However, there is also scope for using qualitative methods, in conjunction with theory and evidence synthesis to identify harms outside of trials.

Where does this leave the approach to recording AEs in these types of interventional trials?

All trials need to acknowledge or assess the likelihood that harms or unintended consequences are possible from behavioral or lifestyle interventions. The obligations to record AEs as required by RECs remain; however, there is a need to support investigators in how to define and assess beyond the ICH GCP definitions. This is essential so that harms recording better reflects the harms attributable to these types of intervention. Consensus on AE definitions and assessment beyond using approaches designed for pharmacological trials is required, which will improve inter-trial consistency on AE recording.

4.1. Limitations

This is a review of trial protocols only. Other study documentation (AE forms, standard operating procedures or oversight committee charters) may provide further details on AE recording.

This is a review of what *was planned* in trials. There is no evidence of whether these protocols were implemented as planned or any difficulties in recording AE data. This was a broad review in terms of trial populations and interventions, aiming to investigate any common approaches in managing AE recording in non-pharmacological trials, since all non-pharmacological trials are obligated to the same REC reporting standards. There will be specific issues for types of behavioral interventions. Indeed, in psychological therapies a number of checklists or alternative definitions of what constitutes an AE are available [86–88].

4.2. Key recommendations for AE recording in trial protocols

1 The level of risk or likelihood of harm from an intervention should always be assessed.
2 Serious AEs should be population and/or intervention specific. Investigators could consider defining AEs as serious beyond the ICH GCP definition.
3 Listing all expected adverse events for the trial populations and intervention is challenging a priori. However, for transparency for SUSAR assessment, a list of expected events should be provided in the protocol. Further research is needed to derive expected AE lists consistently between trials.
4 Exemptions from AE recording may make recording more manageable; however, these should be justified. Excluding non-serious AEs when using the ICH GCP definition may not be appropriate
5 Use of oversight committees may allow ratification of AE recording plans including independent expert input on the list of expected events. During trials there may be a formal role for independent committees to assist with causality assessment.

4.3. Future research

Future research should be directed at supporting investigators moving beyond the definitions and approaches used in pharmacological trials. Of particular importance is how to derive lists of expected events and what might constitute a serious AE for an intervention type or clinical area. Using evidence synthesis to review mechanisms of harms or harm typologies [2,83,89] is required. Evidence synthesis of harms in specific clinical areas may enable production of core adverse outcome sets to enable transparency and consistency across trials of similar interventions. Further published case studies using the "dark logic model" process approach [1] across different disciplines may be useful reference for clinical trial investigators.

5. Conclusion

Monitoring and recording AEs is undertaken with wide variability and a lack of transparency in behavioral, lifestyle and psychological therapy interventions. The reliance on AE definitions and recording approaches originally devised for pharmacological trials risks failure to reflect harms attributable to these intervention types. Future trials should assess the risk and likelihood of harm during intervention development and protocol writing. Consideration of defining serious AEs outside of the ICH GCP definition is required. Expected AEs should be listed in protocols and typologies of harms for behavioral interventions [2,83,89] and "dark logic model" processes [1] may guide this. However, further research is needed to support investigators. Evidence synthesis of mechanisms of harms and on intervention and population specific harms is required. Publication of case studies implementing the processes of deriving expected AEs [1] may be useful. Achieving expert consensus on AE definitions and assessment methods will improve inter-trial consistency.

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Author contributions

Diana Papaioannou: Conceptualization; Investigation; Formal analysis; Visualization; Roles/Writing - original draft; Cindy Cooper: Conceptualization; Writing - review & editing. Cara Mooney: Investigation; Validation; Writing - review & editing. Rachel Glover: Investigation; Validation; Writing - review & editing. Elizabeth Coates: Conceptualization; Writing - review & editing.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.jclinepi.2021.03.002.

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