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REVIEW

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What metrics of harm are being captured in clinical trials involving talking treatments for young people? A systematic review of registered studies on the ISRCTN

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Abstract

Objective: The recording of harm and adverse events in psychological trials is essential, yet the types of harm being captured in trials for talking treatments involving children and young people have not been systematically investigated. The aim of this review was to determine how often harm and adverse events are recorded in talking treatments for children and young people, as well as the metrics that are being collected.

Method: The ISRCTN was searched for trials involving talking therapies and young people. Of 355 entries, 69 met inclusion criteria. The authors of these records were contacted for further information, and additional searches were conducted of protocols and papers.

Results: Findings show that around half of all records mentioned harm or adverse events in at least one piece of study documentation. Overall, metrics commonly collected are as follows: suicide, suicidal ideation and intent, self-harm, changes to clinical symptomology, and the need for further or additional care.

Conclusions: Similar to the wider field of psychological interventions for mental health, the recording of harm and adverse events in children and young people tends to rely on a few key metrics, many of which are borrowed from drug trials. Examples of best practice have been highlighted, as well as recommendations for the progression of this research area.

KEYWORDS

adverse event, children, harm, talking therapy, trial, young people

Practice implications

- Researchers and intervention developers should be mindful of harm and adverse events that can occur during trials.
- When recording harm, individuals should consider metrics, which go beyond death, suicidal ideation/intent, self-harm, changes to clinical symptomology and the need for additional

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care, tailoring metrics both to the intervention and to the population being studied. Some additional metrics are outlined.
- Drawing on routinely collected data, checklists and interviews with participants may help to triangulate harm from different sources.

Policy implication

- Submission of trial protocols should include a clear outline of the adverse events protocol as part of their supplementary information.

1 | BACKGROUND

The role of a Data Monitoring Committee (DMC) is of central importance when conducting clinical trials (Ellenberg et al., 2002). The aims of a DMC include protecting the validity and credibility of a trial, monitoring or assessing the intervention's safety and making recommendations based on these data (DAMOCLES Study Group, 2005). This includes monitoring any evidence of treatment harm as a result of the intervention, and relatedly, whether the trial, or specific intervention arms, should be discontinued (DAMOCLES Study Group, 2005). However, a discrepancy exists between drug trials, where the monitoring of harm is compulsory, and psychological trials, where it is not (Berk & Parker, 2009).

1.1 | Defining adverse events

Within drug trials, the European Clinical Trials Directive defines adverse events as any incident experienced by a trial participant, which:

- is fatal or life-threatening;
- results in inpatient hospital admission or prolongation of existing hospital admission;
- results in persistent or significant incapacity of the patient, or substantially disrupts the patient's ability to perform normal life functions;
- or results in a congenital anomaly/birth defect

(European Parliament and Council of the European Union, 2001; UK Legislation, 2004). Guidance from the US Food and Drug Administration (FDA), as well as the United Kingdom (UK) National Research Ethics Service (NRES), also draws on these criteria.

Translating these conditions to psychological trials may be difficult due to added complexities. Practically, some definitions (e.g. congenital anomaly/birth defect) may not be relevant, and other aspects specific to psychological interventions may be missing (e.g. self-harm). Dimidjian and Holland (2010) outline that psychological trials, by nature of their intervention, differ from drug trials in the following ways:

1. Adverse events are more likely to be related to the therapist rather than a drug. Moreover, therapists have difficulty predicting treatment.
2. The nature of the therapeutic relationship and harm caused by treatment means there could be legal consequences for the therapist.
3. Untangling adverse events from negative events in the patient's life is difficult.
4. Discerning positive and negative effects is challenging due to their subjective nature (e.g. splitting up with a partner could be seen as positive or negative).
5. Due to a lack of procedural guidelines, it is difficult to separate whether the patient may not have had enough 'dosage' from the intervention, or whether the therapist's behaviour has caused the outcome.

It is important to record harm and adverse events in psychological trials (Linden, 2013). Conceptually, it has been argued that talking treatments should not be thought of as categorically 'safe', as any intervention that may benefit a patient could also have detrimental effects (Curran et al., 2019; Parry et al., 2016). Indeed, findings from the psychoeducation with problem-solving (PEPS) study, which aimed to improve social functioning in adults with personality disorder, support this view (McMurran et al., 2011). During this trial, the higher rates of recorded adverse events in the intervention arm led to the DMC recommending that recruitment be halted, which was supported by the Trial Steering Committee (TSC).

1.2 | Defining adverse events from psychological treatment

Within psychological literature, concepts related to harm are often used interchangeably. These include the following: adverse events, side effects, harm, negative events, negative outcomes, unwanted effects, non-intentional effects and treatment failure (Parry et al., 2016). Despite this, attempts have been made to categorise such events. Linden (2013) proposed sixteen domains in which harm and adverse events may occur. These included the following: symptomology, the well-being of the patient, the therapeutic relationship, the patient's social and family networks, and changes in patient circumstances and situations. These have been made into a checklist (UE-ATR checklist; Linden, 2013) with which events can be recorded by clinicians, along with the context they occur in, whether they are believed to be related to the treatment, and the severity of

the event. However, the Linden (2013) framework, whilst useful in helping to identify adverse events from psychological treatments, has limitations. Firstly, it was not developed for use by researchers, rather clinicians. Secondly, it was not developed for use with young people. Thus, in both instances, some domains for recording adverse events may be missing.

1.3 | Harm from psychological treatment

A national survey of adult patients in the UK who attended services for psychological treatment found that 5% reported having experienced a lasting bad effect (Crawford et al., 2016). Furthermore, it was found that both sexual and ethnic minority patients reported bad effects at a higher rate than their majority peers. Conversely, individuals aged 65 and over were less likely to report lasting harmful events (Crawford et al., 2016). Estimates from other studies have focused on specific conditions or treatments. Patients with depression and obsessive–compulsive disorder reported side effects from psychological treatment in 39% and 93% of instances, respectively (Moritz et al., 2015, 2018). Another study focusing on CBT treatment identified negative effects on well-being and increased distress in 27% of patients, a worsening in symptoms in 9% of patients and strains in family relationships in 6% of patients (Schermuly-Haupt et al., 2018). Within this, over a fifth of patients reported these side effects as severe or very severe.

1.4 | Recording harm and adverse events in psychological trials

Reviews exploring the recording of adverse events in psychological trials have previously been undertaken (Duggan, Parry, McMurran, Davidson, & Dennis, 2014; Jonsson et al., 2014; Vaughan et al., 2014). In one review focusing on adults, requests for protocols and final reports were made to the UK National Institute for Health Research (NIHR) (Duggan et al., 2014). It was found that adverse events were not mentioned in any final report evaluating a psychological intervention. Conversely, this was not the case for drug trials. Where adverse events for psychological trials were mentioned in papers, these relied on the NRES guidelines, which were developed for drug trials. The authors concluded that the current reporting of adverse events was inadequate and required refinement for talking therapies.

A further review exploring adverse events in psychological and drug trials also concluded that trials evaluating medications were more likely to mention adverse events (Vaughan et al., 2014). Whilst this review included some studies focused on children and young people, only papers in high-impact journals (>5) were included, and other documentation, such as protocols, was excluded. Moreover, a random subsection of each type of trial was chosen for analysis. These limitations could result in findings that are not generalisable. Another review, released in the same year by Swedish researchers, found that of 132 included records, 28 (21%) mentioned information around harm or adverse events (Jonsson et al., 2016). The most common indicator of harm, clinical deterioration, was captured in 15 trials. This review included psychological interventions with children and young people; however, the majority of records (73%) pertained to adults. Protocols were not included when searching records. Other ongoing research has been identified in this area, but these studies are also restricted to adults (Klatte et al., 2018).

There has been movement towards facilitating the better reporting of trial data in psychological and social trials. Of particular note is the development of the Consolidated Standards of Reporting Trials Statement for Social and Psychological Interventions (CONSORT-SPI) (Grant et al., 2018). Within this, credence is given to adverse events, with recommendations that important adverse events and side effects are captured and reported in journal or conference abstracts. Limitations remain about the definition of an 'important' adverse or harmful event. Without specific guidance on what to look for, researchers, trial managers and clinicians are left to decide which events to capture, which may lead them to miss, disregard or misattribute events to the patient or other factors.

1.5 | Adverse events from psychological treatment for young people

Similar to adults, young people are at risk of harm from psychological treatment. Indeed, there could be even more risk of potential harm due to physical (e.g. developmental capacity) and psychological (e.g. mental capacity) vulnerabilities associated with this life stage (Mercer, 2017). Additionally, young people may feel forced to comply with treatment due to power imbalances between them, their parents/carers and their clinician (Hayes et al., 2015; LeFrançois, 2008).

Additionally, there is concern that programmes for young people with group elements (e.g. for conduct disorder or antisocial behaviour) may provide environments which facilitate high risk or unwanted behaviours (Rhule, 2005). This has been found in programmes such as the Cambridge–Somerville Study (McCord, 1992). Long-term follow-up of individuals in the intervention arm, which consisted of a social worker who provided access to counselling, family therapy, recreational activities and summer camps, found participants were more likely to suffer from alcoholism, be deceased at 35 and have committed a crime than those who were not part of the intervention (McCord, 2003). These effects were dose-dependent, with higher rates of participation in the intervention resulting in a greater likelihood of these negative outcomes (McCord, 2003).

One review explored potentially harmful treatment with four specific adverse childhood experiences: physical hurt or humiliation, physical abuse, and not feeling loved or important (Mercer, 2017). Five harmful therapies were identified: Conditioning/Operant Punishment Using Electric Shocks; Holding Therapy/Attachment Therapy and Diagnosis; Holding Therapy/Attachment Therapy Adjuvant Methods; Festhaltetherapie (Holding Time, Prolonged Parent–Child Embrace); and conversion therapy. However, this

review only explored therapies as a whole, rather than adverse events that can occur due to treatment. Other research, whilst starting to explore the concept of harm, relies solely on clinical settings rather than research trials (Castro Batic & Hayes, 2020; Jonsson et al., 2016). In both these papers, participants were clinicians, meaning again that young people and families' experiences were omitted.

To date, one review has been conducted to explore iatrogenic effects on young people (Werch & Owen, 2002). Focusing on substance abuse programmes in schools, 17 studies met inclusion criteria and 43 instances of negative outcomes were reported. The most common negative outcomes included estimates of substance use, as well as prosocial attitudes towards substances and increased expectations of future use. Whilst providing some initial research into this area, this review is limited to a very specific population, and the intervention is in a non-clinical setting. Thus, how this relates to young people in clinical trials for talking therapies is unknown.

1.6 | Summary and aims

Harm and adverse events are known to occur in psychological trials (Linden, 2013). However, previous reviews have not focused on children and young people (Duggan et al., 2014), have focused on randomly selected studies (Vaughan et al., 2014), have only reviewed final papers, omitting other sources of information such as protocols and trial registries (Jonsson et al., 2014; Vaughan et al., 2014), or have focused on non-clinical populations involving young people (Werch & Owen, 2002). Alongside these reviews, there has been increasing debate around the reporting rates of adverse events in psychological trials (Grant et al., 2018). Thus, the aim of this paper was to undertake a review of how adverse events are captured in psychological trials, focusing on young people and talking therapies. Specific questions include the following:

a. To what extent are harm and adverse events being captured in psychological trials involving children and young people?
b. When captured, what types of adverse events are being recorded?
c. Does there appear to be a difference in the extent to which harm and adverse events are being captured over time?

2 | METHOD

2.1 | Protocol and registration

This review was undertaken as part of an MSc research project and was therefore not eligible to be registered on PROSPERO in line with their guidelines. Instead, an unregistered protocol was produced before work began on this review, which was then reviewed by the postgraduate research supervisory team on the MSc course. The review was carried out in line with the PRISMA checklist (see Appendix A).

2.2 | Eligibility criteria

Search results were limited to the ISRCTN database. This database was chosen because: a) it is a database that is widely used to register psychological trials and is recognised by the World Health Organization (WHO) and ICMJE, and b) researchers are able to register their studies prior to final papers being produced, allowing the authors of this review to monitor where adverse events are first mentioned and whether these are being monitored within ongoing studies.

To be eligible for inclusion, studies were required to meet the following criteria:

1. Young people had to be aged 18 years or younger.
2. Studies could be conducted in any country, but they had to be registered on the ISRCTN database.
3. Studies had to be written in English.
4. Intervention or treatment had to be a form of talking therapy. This was defined as an intervention that involved talking with a trained therapist or clinician to improve mental health or well-being (NICE, 2018). Interventions where the main component or one of the main components of the intervention was not a talking therapy (e.g. parent training or solely drug treatment) were excluded.
5. Harm, risk and adverse events were captured at any point during the active intervention or follow-up study period.

2.3 | Information sources and search

The ISRCTN database was searched until May 2020. Records registered and approved by the ISRCTN before this date were eligible for inclusion. Records were filtered on the central database to include only 'mental and behavioural disorders' and 'child'. This resulted in 355 records.

2.4 | Record selection and data extraction

The two authors of this paper (DH and NZ) independently reviewed all records for inclusion in this review. A good interrater reliability was obtained (0.79), and any disagreement was resolved by discussion and consensus. This resulted in 69 records being eligible for inclusion. Figure 1 shows reasons for exclusion, with the main reason being the intervention was not a talking therapy ($n = 274$).

Following this, data were extracted from each included record on the ISRCTN registry using a data extraction tool. This tool included the following: the primary and senior author's names and contact details, which documentation had been linked to the ISRCTN (protocols and papers) and whether there was any mention of harm and adverse events. Where any additional documentation was available, this was reviewed and the following data were extracted: year and country where the study was conducted, intervention, age range of participants, mental health difficulty, whether the documentation mentioned harm or adverse events, and whether specific metrics on harm or adverse events were recorded.

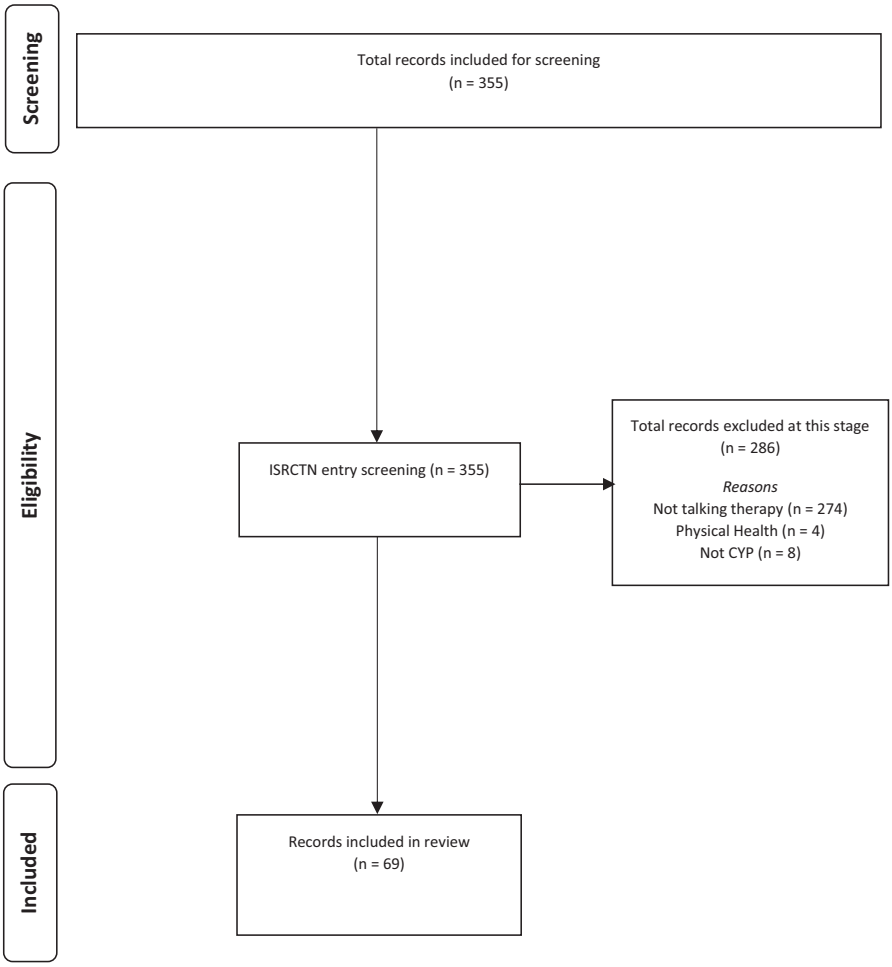

FIGURE 1 Flow chart for screening and included records

Where additional documentation was not readily available, authors were contacted and asked to provide any protocols and papers. The same data extraction process took place for any additional included documents. All data extraction was undertaken by one author (NZ) with the other author (DH) reviewing 20% of the sample.

2.5 | Ethical approval

Ethical approval was not needed for this study as it relied on synthesising information from registries, papers and protocols.

3 | RESULTS

3.1 | Characteristics of included records

Records dated from 1994 to 2017. Table 1 outlines record characteristics. Overall, 86% (n = 59) of studies were conducted in Europe. Records spanned a wide range of mental health difficulties; however, the most common difficulty under investigation was anxiety disorders (38%, n = 28). The most frequently tested psychological intervention was cognitive behavioural therapy (64%, n =44). Study follow-up periods ranged from immediately after the end of the intervention to 24 months post-intervention (modal follow-up: 12 months).

3.2 | To what extent are harm and adverse events being captured in psychological trials involving young people?

When reviewing study documentation, 52% of records (n = 36) mentioned harm or adverse events in at least one piece of documentation. Each data source (ISRCTN entries, protocols and papers) will be independently discussed below.

3.3 | Where monitored, what types of harm and adverse events are being recorded and where[1]?

3.3.1 | ISRCTN entries

For the 69 ISRCTN entries that met inclusion criteria, 52% (n = 36) left the section around risks, harm and adverse events blank, and 48% (n = 33) filled this section out. For those where written text was present, 43% (n = 16) explicitly referenced that there were no known risks

associated with taking part in the study, whilst 57% ($n = 17$) referred to specific metrics.

The most common metric referenced changes in negative emotions (61%, $n = 11$). These included 'increased distress' and 'discomfort', which were mentioned in nine studies (2, 3, 13, 15, 18, 19, 21, 23 and 27), and 'negative emotions', which were mentioned in two studies (7 and 11). Two entries outlined there were risks associated with taking part but did not specify what these were (48, 49). Additional entries focused on aspects such as medication side effects (1), questionnaire burden (10), the unknown effect of treatment (14), and risks associated with the patients suffering from anorexia nervosa, the disorder that the intervention was targeting (55).

3.3.2 | Protocols

Forty-one per cent ($n = 28$) of the 69 ISRCTN entries had protocols. This included 23 published protocols, four unpublished protocols and one record that had both.

Of the 28 available protocols, 39% ($n = 11$) did not mention harm or adverse events. The remaining 61% ($n = 17$) did provide some information on this. Of these, eight did not specify which adverse events would be recorded but outlined that they had an adverse event procedure in place. No further information was available from authors when requested. One additional protocol outlined that no events were expected to occur due to previous work undertaken.

For those that did discuss specific metrics ($n = 8$), these could be grouped into five overarching areas: death, suicidal ideation/intent, the patient needing further/additional care, changes to clinical symptomology and other. These will be discussed below:

Death

Three protocols outlined that death was a specific metric they intended to capture (5, 6, 46). Two protocols outlined this as 'death' (6, 46), whilst the other was more specifically referring to 'suicide' (5).

Suicidal ideation/intent

Two protocols referenced plans or thoughts for an individual to end their life as a metric they intended to capture (2, 31). In one, this was referred to as 'suicidal behaviour' (2), whilst in the other, this was referred to as a 'suicide attempt' (31). The other two protocols were vague but defined 'life-threatening' events as metrics they intended to capture (e.g. 5, 6).

Further/additional care

Five protocols outlined that they intended to capture the patient needing enhanced or further care (2, 5, 6, 31, 46). In one protocol, this included 'being sectioned' or 'admission to psychiatric hospital' (2). In two others, this included 'hospitalisation or prolonged hospitalisation' or the patient having a 'persistent significant disability or incapacity' (5, 6). A third referenced a patient needing 'psychiatric consultations' (31), whilst another included 'hospital admissions', 'emergency outpatient attendance' and 'referral to mental health services' (46).

Changes in clinical symptomology

The metric 'changes to clinical symptomology' was captured in three protocols. In one, this included the following: 'deterioration', 'a new mental health diagnosis', 'distress from therapy', 'a sustained and significant increase in detrimental behaviours (e.g. self-harm)' and 'emergence of new detrimental behaviours' (2). One other protocol referred to 'deterioration' (7), whilst another referenced 'changes in parent or child mental health status' and 'deterioration in child behaviour' (37).

Other

Two protocols referenced other metrics for harm and adverse events that they planned to capture (2, 5). In one, it was acknowledged that these metrics, despite potentially being indirectly related, would be recorded: 'safeguarding issues revealed', 'school/work affected', 'exclusion/inclusion criteria became unmet', 'dropout of treatment/request to change therapist occurs', 'any actual or potential breach of confidentiality' and a 'complaint received around any potential adverse event' (2). The other protocol referenced 'a congenital anomaly or birth defect' (5) as one type of adverse event.

3.3.3 | Peer-reviewed papers

For the 69 ISRCTN records, nine were reported as ongoing or complete without papers (as these were currently being written or were undergoing peer review). The authors of the remaining 60 records were contacted and databases searched; 22% ($n = 13$) did not yield papers through author contact or literature searching, which left 78% ($n = 47$) of studies with available papers.

Of the 47 available peer-reviewed papers, 68% ($n = 32$) did not mention harm or adverse events. The remaining 32% ($n = 15$) provided some information on harm or adverse events. For five papers, an adverse events procedure was mentioned, but specific metrics were not discussed (19, 26, 45, 57, 61). No further information on this was available from authors.

The same overarching headings employed previously are used to discuss findings below.

Death

Two papers outlined that death was a specific metric they captured (43, 46). One paper outlined that no suicide attempts were recorded during the trial (43). Similarly, the other paper recorded that no deaths were reported (46).

Suicidal ideation/intent

Six papers outlined that suicidal ideation/intent was a specific metric they captured (22, 24, 35, 42, 55, 69). In one paper, an overdose was recorded in the control arm of the study (22), whilst in another study, two participants attempted suicide by overdose

TABLE 1 Characteristics of included records

Ref number	ISRCTN entry	Country/ Countries	Trial start date	Talking therapy examined	Mental health difficulty examined	Is medication part of the treatment protocol?	ISRCTN entry discusses risk, harm or adverse events
1	ISRCTN92640175	Romania	2006	1. Psychotherapy: CBT / rational emotive behaviour therapy 2. Medication (atomoxetine) 3. Combined treatment	ADHD	Y	Y
2	ISRCTN86123204	United Kingdom	2017	1. Adolescent cognitive treatment for anxiety 2. Control treatment: established group therapy	Anxiety	N	Y
3	ISRCTN81736780	United Kingdom	2016	Cognitive Remediation Therapy	Anorexia	N	Y
4	ISRCTN73367465	Netherlands	2015	Cognitive Bias Modification for Interpretation	Anxiety	N	Y.
5	ISRCTN85369879	United Kingdom	2015	1. Imagery-based cognitive behavioural intervention 2. Non-directive supportive therapy	Depression	N	Y
6	ISRCTN19883421	United Kingdom	2016	Intervention group: one session treatment (variant of CBT based interventions, but a more condensed approach) Control group: CBT	Anxiety	N	Y
7	ISRCTN17366720	Sweden	2015	1. Dialectical behavioural therapy 2. Psychoeducational intervention	ADHD	N	Y
8	ISRCTN13078441	Netherlands	2014	Power Coaching: A multiple-domain CBT coaching programme	ADHD	N	Y

Types of risk, harm or adverse events discussed (if any)	Protocol available	Protocol discusses risk, harm or adverse events	Types of risk, harm or adverse events discussed	Peer-reviewed paper available	Paper discusses risk, harm, or adverse events	Types of risk, harm or adverse events discussed
Adverse medication effects	N	-	–	N [O]	-	-
Distress or discomfort	Y [P, U]	Y [P, U]	Deterioration, Being sectioned, Admission to psychiatric hospital, New mental health diagnosis, Suicidal behaviour, Safeguarding issues revealed, School/work affected, Therapy causes unacceptable distress, Exclusion/inclusion criteria become unmet, A sustained and significant increase in detrimental behaviours, Emergence of new detrimental behaviours, Dropout of treatment / request to change therapist. Any actual or potential breach of confidentiality, Complaint received around any potential adverse event	N [O]	N	-
Distress	Y [P]	N	-	N [O]	-	-
None known	N	-	-	Y	N	
None known	Y [P]	Y [P]	An event that: is life-threatening, or results in hospitalisation or prolongation of existing hospitalisation, persistent or significant disability or incapacity, and a congenital anomaly or birth defect. Self-harm, Suicide	N [O]	-	-
None known	Y [P]	Y	Life-threatening, or require hospitalisation or prolongation of existing inpatient stay, or result in persistent or significant disability or incapacity or death	N [O]	-	-
Negative emotions Stigma	Y [P]	Y [P]	Deterioration	N [O]	-	-
None known	N	-	-	N	-	-

(Continues)

TABLE 1 (Continued)

Ref number	ISRCTN entry	Country/ Countries	Trial start date	Talking therapy examined	Mental health difficulty examined	Is medication part of the treatment protocol?	ISRCTN entry discusses risk, harm or adverse events
9	ISRCTN13721202	United Kingdom	2015	CBT	Anxiety	N	Y
10	ISRCTN24029895	Norway	2015	CBT and parental training	Multiple/ unspecified	N	Y
11	ISRCTN19700389	Norway	2014	Adolescent coping with depression course based on CBT, rational emotive behaviour therapy, meta-cognitive theory and positive psychology	Depression	N	Y
12	ISRCTN59518816	Australia	2015	CBT	ADHD	N	Y
13	ISRCTN21802136	United Kingdom	2015	CBT for psychosis	Multiple/ unspecified	N	Y
14	ISRCTN52147450	United Kingdom	2014	1. Behavioural activation therapy 2. Treatment as usual—treatment deemed necessary by their clinician	Depression	N	Y
15	ISRCTN11333815	Germany	2014	Manualised psychodynamic short-term psychotherapy	Anxiety	N	Y
16	ISRCTN32083735	United Kingdom	2014	Child development education and solution-focused therapy	Multiple/ unspecified	N	Y
17	ISRCTN44253140	United Kingdom	2013	School-based person-centred counselling / humanistic psychological therapy	Multiple/ unspecified	N	N
18	ISRCTN35018680	United Kingdom	2013	Trauma-focused CBT	Anxiety	N	Y
19	ISRCTN67079741	Canada	2013	Cognitive behavioural social skill group intervention	Autism	N	Y
20	ISRCTN33930984	Australia	2013	CBT	ADHD	N	Y
21	ISRCTN52310507	Sweden	2010	Support group intervention	Multiple/ unspecified	N	Y
22	ISRCTN13766770	United Kingdom	2011	CBT	Multiple/ unspecified	N	Y
23	ISRCTN65340805	United Kingdom	2013	Psychodynamic therapy	PTSD	N	Y

Types of risk, harm or adverse events discussed (if any)	Protocol available	Protocol discusses risk, harm or adverse events	Types of risk, harm or adverse events discussed	Peer-reviewed paper available	Paper discusses risk, harm, or adverse events	Types of risk, harm or adverse events discussed
None known	Y [U]	N	-	N	-	-
Questionnaire burden	Y [P]	Y [P]	Does not specify specific events, only AE procedure	N [O]	-	-
Negative emotions	Y [P]	Y [P]	Does not specify specific events, only AE procedure	Y	N	-
None known	Y [P]	-Y	No adverse effects foreseen	N [O]	-	-
Distress or discomfort	Y [P]	Y [P]	Does not specify specific events, only AE procedure	N	-	-
Unknown effectiveness of treatment Interview burden	N	-	-	N [O]	-	-
Increase distress (control group)	N	-	-	N	-	-
None known	Y [P]	N	-	N	-	-
-	N	-	-	Y	N	
Discomfort or distress	Y [P]	Y [P]	Does not specify specific events, only AE procedure	N	-	-
Distress or discomfort Questionnaire burden	N	-	-	Y	Y	Does not specify specific events, only that no participants experienced harm
None known	Y [P]	Y [P]	Do not anticipate any adverse events	Y	N	-
Distress or discomfort	Y [P]	N [P]	-	N	-	-
None known	N	-	-	Y	Y	Deterioration in the young person's mental health or welfare, Attempted self-harm/suicide Identified social care need.
Distress or discomfort Deterioration	N	-	-	N	-	-

(Continues)

TABLE 1 (Continued)

Ref number	ISRCTN entry	Country/ Countries	Trial start date	Talking therapy examined	Mental health difficulty examined	Is medication part of the treatment protocol?	ISRCTN entry discusses risk, harm or adverse events
24	ISRCTN67699666	United Kingdom	2012	CBT	BDD	N	N
25	ISRCTN31234060	Germany	2011	Brief motivational intervention (counselling session)	Drug abuse/ misuse	N	Y
26	ISRCTN07627865	United Kingdom	2012	1. Guided CBT self-help 2. Solution-focused brief therapy	Anxiety	N	Y.
27	ISRCTN58027256	Sweden	2012	1. Trauma-focused CBT 2. Attachment-based family therapy	Anxiety	N	Y
28	ISRCTN92977593	United Kingdom	2008	Guided CBT self-help	Anxiety	N	Y
29	ISRCTN33871591	Chile	2010	CBT	Depression	N	Y
30	ISRCTN90251787	Germany	2010	Family-based prevention	Drug abuse/ misuse	N	N
31	ISRCTN19466209	Chile	2009	CBT	Depression	N	N
32	ISRCTN23563048	United Kingdom	2011	CBT	Anxiety	N	N
33	ISRCTN79049138	Australia	2009	1. Family-focused CBT 2. Child-focused CBT	PTSD	N	N
34	ISRCTN25252940	United Kingdom	2003	Reflective Interpersonal Therapy for Children and Parents	Conduct problems	N	N
35	ISRCTN50951795	United Kingdom	2009	Cognitive therapy	Anxiety	N	N
36	ISRCTN27650478	United Kingdom	2008	Functional family therapy	Conduct problems	N	*N*
37	ISRCTN11219568	United Kingdom	2009	CBT	Anxiety	N	N
38	ISRCTN38352118	United Kingdom	2010	CBT	PTSD	N	Y
39	ISRCTN30996662	Australia	2010	Parenting intervention	Anxiety	N	N
40	ISRCTN51014277	Belgium; France; Germany; Netherlands; Switzerland	2007	Multidimensional family therapy	Drug abuse/ misuse	N	N
41	ISRCTN27026136	United Kingdom	2010	Counselling	Multiple/ unspecified	N	N

Types of risk, harm or adverse events discussed (if any)	Protocol available	Protocol discusses risk, harm or adverse events	Types of risk, harm or adverse events discussed	Peer-reviewed paper available	Paper discusses risk, harm, or adverse events	Types of risk, harm or adverse events discussed
-	N	-	-	Y	Y	Attempted suicide
None known	Y [P]	N [P]	-	Y	N	-
None known	N	-	-	Y	Y	Does not specify specific events, only that no participants experienced harm
Distress or discomfort	N	-	-	N	-	-
None known	N	-	-	Y	N	-
None known	N	-	-	Y	N	-
-	Y [P]	N [P]	-	Y	N	-
-	Y [P]	Y [P]	Suicide attempts, Psychiatric consultations	Y	N	-
-	Y [P]	N [P]	-	Y	Paper 1 – N Paper 2 - N	-
-	Y [P]	N [P]	-	N	-	-
-	N	-	-	*N*	-	-
-	N	-	-	Y	Y	Dropout due to discomfort of focusing on symptoms Suicidal thoughts
-	N	-	-	Y	N	-
-	Y [U]	Y [U]	Change in parent or child mental health status, Deterioration in child behaviour	Y	N	-
None known	Y [U]	Y [U]	Does not specify specific events, only AE procedure	Y	N	-
-	Y [P]	Y [P]	Does not specify types of harm	Y	N	-
-	Y [P]	N [P]	-	Y	Paper A – N Paper B - N	-
-	N	-	-	Y	N	-

(Continues)

TABLE 1 (Continued)

Ref number	ISRCTN entry	Country/ Countries	Trial start date	Talking therapy examined	Mental health difficulty examined	Is medication part of the treatment protocol?	ISRCTN entry discusses risk, harm or adverse events
42	ISRCTN83033550	United Kingdom	2009	1. Short-term psychoanalytic psychotherapy 2. CBT	Depression	Y—allowed to prescribe fluoxetine	N
43	ISRCTN20496110	United Kingdom	2002	Group therapy	Self-harm	N	N
44	ISRCTN77132214	United Kingdom	2009	Multisystemic therapy	Young people 'at risk'	? Treatment needs vary	Y
45	ISRCTN70977225	United Kingdom	2009	CBT	OCD	Y	N
46	ISRCTN59793150	United Kingdom	2009	Family therapy	Self-harm	N	Y
47	ISRCTN27070832	United Kingdom	2008	CBT	OCD	N	N
48	ISRCTN66385119	Denmark; Norway; Sweden	2008	1. CBT 2. Sertraline	OCD	Y	Y
49	ISRCTN95266816	United Kingdom	2008	1. Psychotherapy using the mentalisation based treatment approach 2. Family therapy based on short-term mentalisation and relational therapy 3. Group Therapy	Self-harm/ BPD	N	Y
50	ISRCTN19083628	United Kingdom	2008	Group CBT	Depression	N	N
51	ISRCTN05595708	United Kingdom	2006	CBT	PTSD	N	N

Types of risk, harm or adverse events discussed (if any)	Protocol available	Protocol discusses risk, harm or adverse events	Types of risk, harm or adverse events discussed	Peer-reviewed paper available	Paper discusses risk, harm, or adverse events	Types of risk, harm or adverse events discussed
-	Y [P]	Y [P]	Does not specify specific events, only AE procedure	Y	Y	Physical adversities including breathing problems, sleep disturbances, drowsiness tiredness, nausea, sweating, restlessness overactivity Suicidal ideation, non-suicidal self-injury, Suicide
-	N	-	-	Y	Y	Suicide Other recorded death Self-harm
None known	Y [P]	N [P]	-	Y	N	-
-	N	-	-	Y	Y	Does not specify specific events, only that no participants experienced harm
None known	Y [P]	Y [P]	Death, Hospital admissions, Emergency outpatient attendance, Referral to mental health services	Y	Y	Death Hospital admissions Attendance at accident and emergency Referral to mental health services
-	N	-	-	Y	Paper A—N Paper B - N	-
Risks (unspecified)	N	-	-	Y	Paper A—*N* Paper B—*N* Paper C—*N*	-
Risks (unspecified)	N	-	-	Y	*N*	-
-	Y [P]	N [P]	-	Y	Paper A—Y Paper B—N Paper C—*N*	Increased symptomology
-	Y [U]	Y [U]	Does not specify specific events, only outlined events will be reported to steering group	Y	N	-

(Continues)

TABLE 1 (Continued)

Ref number	ISRCTN entry	Country/ Countries	Trial start date	Talking therapy examined	Mental health difficulty examined	Is medication part of the treatment protocol?	ISRCTN entry discusses risk, harm or adverse events
52	ISRCTN97589104	Netherlands	2007	Emotion regulation training	BPD	N	N
53	ISRCTN11275465	United Kingdom	2003	Family therapy	Anorexia	? Therapeutic input as required	N
54	ISRCTN07286192	Netherlands	2006	Brief trauma-focused CBT	PTSD	N	N
55	ISRCTN67783402	Germany	2006	1. Occupational therapy 2. Nutritional counselling 3. Nutritional therapy 4. Group therapy 5. CBT 6. Family-based therapy 7. Medication management	Anorexia	Y	Y
56	ISRCTN46352117	Netherlands	2006	CBT	Anxiety	N	N
57	ISRCTN07851536	Netherlands	2006	CBT	OCD	N	N
58	ISRCTN75187865	United Kingdom	1998	Cognitive remediation therapy	Schizophrenia	N	N
59	ISRCTN72046738	Canada	2002	CBT	Anxiety	N	N
60	ISRCTN48511871	Netherlands	2002	1. Individual cognitive behavioural treatment 2. Group CBT	Anxiety	N	N
61	ISRCTN88858028	Canada	2004	CBT	Multiple/ unspecified	N	N
62	ISRCTN43681784	Australia	2004	Group psychotherapy based on problem-solving and CBT	Self-harm	N	N
63	ISRCTN29092580	United Kingdom	2003	CBT	OCD	N	N
64	ISRCTN44198137	United Kingdom	1997	Group therapy	Self-harm	N	N
65	ISRCTN05516741	United Kingdom	1994	1. Parent training 2. Parent counselling and support	ADHD	N	N
66	ISRCTN54248464	United Kingdom	1999	CBT	OCD	N	N
67	ISRCTN34861010	United Kingdom	2000	Trauma discussion	PTSD	N	N

Types of risk, harm or adverse events discussed (if any)	Protocol available	Protocol discusses risk, harm or adverse events	Types of risk, harm or adverse events discussed	Peer-reviewed paper available	Paper discusses risk, harm, or adverse events	Types of risk, harm or adverse events discussed
-	N	-	-	N	N	-
-	N	-	-	Y	N	-
-	N	-	-	N	-	-
Risks associated with illness (anorexia)	N	-	-	Y	Paper A—Y Paper B—N	Suicidal ideation/ Suicide attempt
-	N	-	-	Y	N	-
-	N	-	-	Y	Y	Does not specify specific events, only that no participants experienced harm
-	N	-	-	Y	N	-
-	N	-	-	Y	N	-
-	N	-	-	Y	N	-
-	N	-	-	Y	Y	Does not specify specific events, only that no participants experienced harm
-	N	-	-	Y	N	-
-	N	-	-	Y	Y?	Effects from ending treatment early (unspecified)
-	N	-	-	Y	N	-
-	N	-	-	Y	N	-
-	N	-	-	Y	N	-
-	N	-	-	Y	N	-

(Continues)

TABLE 1 (Continued)

Ref number	ISRCTN entry	Country/ Countries	Trial start date	Talking therapy examined	Mental health difficulty examined	Is medication part of the treatment protocol?	ISRCTN entry discusses risk, harm or adverse events
68	ISRCTN39345394	United Kingdom	2000	1. Inpatient psychiatric treatment—individual supportive or cognitive therapies and family therapy 2. Specialised outpatient treatment—motivational interview, individual CBT plus parental feedback, parental counselling, dietary therapy and multimodal feedback and monitoring 3. Multidisciplinary family-based approach, individual supportive therapy	Anorexia	? Inpatient treatment unclear	N
69	ISRCTN83809224	United Kingdom	2000	1. Brief initial educational / supportive intervention 2. CBT 3. Fluoxetine	Depression	Y	N

Abbreviations: -, not applicable; ADHD, attention-deficit/hyperactive disorder; BDD, body dysmorphic disorder; BPD, borderline personality disorder; N, No; O = paper not available due to trial ongoing or paper under review; OCD, obsessive–compulsive disorder; P, published protocol; PTSD, post-traumatic stress disorder; U, unpublished protocol; Y, Yes.

(one participant in each arm of the trial) (24). Another paper described one instance of suicidal ideation, which occurred in the intervention arm (35). A further paper outlined three recorded instances of suicidal ideation (one in each arm of the three-armed trial) (42). In another paper, five instances of suicidal ideation were recorded (methods unspecified). This was broken down into three instances in the control arm and two in the intervention arm (55). Lastly, another paper outlined that five participants were withdrawn from the study due to suicide or self-harm (69).

Changes in clinical symptomology

Six papers mentioned negative changes in clinical symptomology (22, 35 42, 43, 50, 69). In one paper, the authors mentioned higher rates of depressive symptoms at follow-up compared with the control arm (50), whilst in another, deterioration was mentioned in that no reliable deterioration was found (22). One further paper explained that five participants were withdrawn from the study due to no reliable improvement (69). One additional paper recorded an instance where a participant dropped out due to discomfort when focusing on clinical symptoms (35).

In two other instances, self-harm was mentioned (42, 43). One paper recorded three instances of self-harm (two in the control arm and one in the intervention arm) (43). The other reported that there was no increase in non-suicidal self-injury as a result of the trial (42).

Additional/further care

Two papers reported on harm and adverse events pertaining to additional/further care (22, 46). In one paper, there was one instance of an identified social care need (unspecified) in the control arm, which resulted in the participant withdrawing consent (22). In the intervention arm of the same study, it was recorded that a participant was readmitted to psychiatric hospital (22). In the other paper, 121 re-referrals to child and adolescent mental health services (CAMHS) were recorded (58 in the intervention arm and 63 in the control arm) (46). The same paper also reported on attendance to accident and emergency (409 events in the intervention arm versus 372 in the

Types of risk, harm or adverse events discussed (if any)	Protocol available	Protocol discusses risk, harm or adverse events	Types of risk, harm or adverse events discussed	Peer-reviewed paper available	Paper discusses risk, harm, or adverse events	Types of risk, harm or adverse events discussed
-	N	-	-	Y	N	-
-	N	-	-	Y	Paper A – Y Paper B – N Paper C - N	Paper 2007— P.6.- Some 59% (61/103) in the SSRI-alone group and headaches, nausea, tiredness, dry mouth, reduced appetite. Irritability disinhibition Suicide Self-harm No improvement

control arm), as well as attendance to a walk-in centre (45 events in the intervention arm versus 89 in the control arm).

Other

Two further metrics of harm and adverse events were mentioned in three additional papers (42, 63 and 69). One metric focused on physical symptoms (42, 69). In one paper, a mean physical adversity score was calculated from physical symptoms such as breathing problems and sleep disturbances (42). The paper noted that compared with baseline, the mean physical adversity scores decreased across all three treatment arms, starting with a score between 5.00 and 5.01 at baseline compared with a follow-up score of between 3.2 and 3.4 (42).

In the second paper, where medication alone was compared with medication with a talking treatment, physical side effects were reported in 61 participants and 65 participants in each arm, respectively. A seizure was mentioned as an adverse event potentially caused by the medication, whilst other 'common' physical side effects included the following: headaches, nausea, dry mouth, tiredness and reduced appetite. Irritability was reported in eight patients and disinhibition in one patient (arms not specified).

In the third paper, the authors outlined that potential harm may have been caused as a result of ending intensive talking therapy, but they noted that clinical scores did not differ at the final point of assessment (63).

3.4 | Does there appear to be a difference in the extent to which harm and adverse events are being captured over time?

To explore whether there were changes over time in whether risks, harm or adverse events were mentioned, results were split into whether they appeared pre-2015 or from 2015 onwards. These dates were chosen as they correspond to when the three previous reviews were published, as well as being one year after the work on

harm in therapy by Linden et al. (2013). A chi-square test of independence showed that there was no significant association between study dates and whether risks, harm and adverse events were mentioned, X^2 (2, $N = 69$) = 0.40, $p = .53$.

4 | Discussion

The aim of this review was to examine the extent to which harm and adverse events are being captured in psychological trials for talking therapies involving children and young people, as well as the types of metrics that are being recorded and whether recording has changed over time. This review was needed as to date, similar studies have either focused solely or largely on adult populations (Duggan et al., 2014; Jonsson et al., 2014; Vaughan et al., 2014) or classroom-based programmes around children and young people's substance use (Werch & Owen, 2002). This highlights a gap in research around adverse events for talking therapy trials involving children and young people, which is particularly important to explore as there are unique considerations when working with this group (Mercer, 2017; Ruhe et al., 2015).

To establish the extent to which harm and adverse events were being captured, the ISRCTN registry and available study documentation were explored. Drawing together all available information, it was determined that 51% of records mentioned harm or adverse events in at least one piece of documentation. In terms of where harm or adverse events were likely to be mentioned, 25% of ISRCTN entries captured metrics pertaining to risks, harm or adverse events. For protocols, 61% mentioned harm or adverse events, and for published papers, this figure was 32%.

Compared with the Duggan et al. (2014) review, this study found a higher percentage of protocols containing information about adverse events (46% versus 61%). Reasons for this are unclear, but this may be due to the acknowledged additional vulnerability of this population and the need to put additional safeguards in place to protect them from harm (Mercer, 2017). Whilst this is initially encouraging, it is important to note that this still leaves a fair proportion of available protocols without any such reporting. A recommendation of this review is that authors should include an explicit, clear and transparent process for monitoring and recording adverse events, which should be submitted as supplementary information alongside peer-reviewed protocols. This will allow for events to be defined from the outset, rather than spontaneous reporting, which can lead to the under-recording of adverse events (Horigian et al., 2010).

The next question sought to understand which types of adverse events and harm were being captured in trials. For ISRCTN entries, these were predominantly in relation to the possibility of increased distress or discomfort from taking part, whilst in protocols and papers, metrics captured included death/suicide, suicidal ideation/intent, changes to clinical symptomology and further/additional care.

The need for further/additional care was the most common set of metrics intended to be captured in protocols. This focused on patients being re-referred to services, sectioned or attending a primary care facility. Conversely, suicidal ideation and intent and changes to clinical symptomology were the metrics most commonly reported when discussing adverse events in papers. Differences between what is intended to be reported and what actually ends up being reported again highlight the need for robust and transparent procedures from the trial outset. It may be that no cases were found for specific adverse events, and this is why these were not reported. However, in line with recommendations from others, all adverse events that are intended to be captured should be reported on, even if no cases are identified (Duggan et al., 2014; Grant et al., 2018).

Metrics found in this review, such as death and suicide and additional/further care, reflect what is reported in other reviews (Duggan et al., 2014; Jonsson et al., 2014). These metrics are closely related to those that are standardly reported on in physical health trials and are mandated by organisations such as the European Clinical Trials Directive, the United States Food and Drug Administration (FDA) and the UK NRES. Whilst adverse event protocols and procedures are more pertinent to pharmacological trials, these are likely to permeate through to psychological trials as no additional standards or metrics have been set (Duggan et al., 2014).

The last question set out to examine whether there were differences over time in whether harm, risks or adverse events were recorded. Results showed there did not appear to be any differences between groups. This differs from Duggan et al. (2014) who found a slight improvement in the reporting in adult trials over time. However, as noted by Duggan et al. (2014), changes to procedures take time. As such, it may be that previous work has had little influence on child and youth mental health research to date. The development of the CONSORT-SPI (Grant et al., 2018) may have an impact in due course.

Importantly, there was acknowledgement within the records and documentation studied (e.g. Goodyer et al., 2017), as well as through contact with authors of included records, that current definitions and procedures for capturing harm and adverse events for psychological trials are suboptimal. Whilst the capturing of events such as suicide, suicidal intent/ideation and self-harm is important, these should form a baseline which intervention evaluators should add to, taking into account the considerations of the intervention and population in question (Duggan et al., 2014). Examples of this have been seen in the review exploring adverse events in classroom-based substance abuse programmes, which included aspects such as increased alcohol and cigarette consumption, as well as changes to self-efficacy (Werch & Owen, 2002). Whilst some attempts have been made to rectify this within clinical settings, albeit not specifically for young people (e.g. Linden, 2013), they have not been successfully translated to research settings. This may be because they were developed for use by clinicians or may be difficult to use.

Despite this, there are some excellent examples of practice. One study protocol exploring the impact of cognitive treatment for anxiety went beyond the basic criteria used in drug trials by including specific areas related to mental health (e.g. diagnosis of a new mental health difficulty), as well as contextual factors (e.g. whether the child or young person's schooling or parent/guardian's work is adversely effected) (Taylor et al. n.d.).

Another good example of practice is the SHIFT trial, which explored family therapy versus treatment as usual for helping young people who had self-harmed (Cottrell et al., 2018). Whilst metrics in this trial were more limited, this trial utilised NHS Digital to obtain adverse event information. Given that unstructured means of collecting data have been shown to yield lower reporting of adverse events in research trials (Horigian et al., 2010), the use of routinely collected data supplemented by other types of information could be beneficial.

Whilst this study is the first to review how harm and adverse events are recorded in trials involving talking therapies for children and young people, it is not without its limitations. One of these is the use of the ISRCTN registry. Only drawing on this database means that trials registered elsewhere may have been missed, which in turn may have affected findings. Furthermore, there is a cost associated with registering trial protocols to the ISRCTN. This means that studies/institutions with less financial resources, as well as some small scale and pragmatic RCTs, may not have been included.

A second limitation is the response rate and detail of available documentation provided. Other than the ISRCTN entries, which provided a baseline to work from, some study documentation was not available to review. Without a full set of study documentation to work from for each included record, findings presented here may not accurately reflect the frequency of harm and adverse events being captured and recorded. This includes whether events when captured were deemed likely (or unlikely) to be related to the intervention, as well as how, if at all, questionnaires used in studies contributed to any adverse event protocols.

The call for a more transparent process in the reporting and monitoring of adverse events in psychological trials, such as by using the CONSORT-SPI (Grant et al., 2018), is welcome. In line with this, the correlation between journal impact and the reporting of adverse events in papers has previously been documented, with higher impact journals being more likely to report adverse events (Vaughan et al., 2014). All journals reporting on trials and pilot studies should consider the reporting and monitoring of adverse events as part of standard practice. However, to be able to do this, researchers and academics first need to know what they should be recording, ideally beyond standardised metrics developed for drug trials. Future research should begin to map out what harm means to children, young people and other stakeholders, and the different metrics that could be captured.

This review provides the first account of the current metrics of harm and side effects being monitored for trials involving talking therapies for children and young people. Even in this context, most metrics tend to be limited to only the most severe types of harm and closely linked to those included in drug trials. To move this field forward, there is a need to develop a comprehensive understanding of the types of harm and side effects therapy can cause, and to ensure that harm and adverse events are described and collected in all studies. This could be achieved through consultation with a wide range of stakeholders, including with young people and their families, via methods such as interviews, focus groups and Delphi studies.

Until this progression has been established, researchers should include additional metrics such as reasons for treatment dropout, self-stigmatisation, changes in the young person's social network and changes/strains in family relationships or behaviours (Linden, 2013; Taylor et al., 2019). Additional metrics researchers may wish to include could focus on the prolongation of treatment and becoming overly dependent on the therapist (Linden, 2013) These could be recorded via questionnaires, as well as by talking to the young person and other stakeholders (e.g. parents). In some instances, it may also be possible to link in with schools and educational systems where consent is given to see educational metrics.

Some academics have cautioned against the over-recording of information around harm or adverse events, citing issues such as burden and cost (Duggan et al., 2014). Whilst these are important points, it may also be argued that until the academic communities understand how talking treatments can harm, the over-recording of harm and adverse events is necessary to safeguard unnecessary suffering of children and young people. This is particularly important if such therapies are subsequently rolled out in clinical settings. Once harm and adverse events are more concretely understood, researchers may then wish to move to a core set of metrics across all psychological therapies, with potential adjuncts for specific treatments, interventions or populations.

CONFLICT OF INTEREST

The authors report no conflict of interest.

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ENDNOTE

[1] From this point forward, in the rest of the results, references used will refer to the table and row relating to the specific ISRCTN entry. This is due to the numbers of documents involved. See the supplementary information for more information and links to all study documentation.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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