Title: Developing and piloting a standard framework tool to assess risk of contamination in psychological therapy trial protocols in mental healthcare

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Abstract

Objective: The objective of this study was to develop and pilot a standard framework which could be used to assess risk of contamination in psychological therapy trials, at the protocol development stage.

Study Design and Setting: We developed and piloted a risk of contamination framework on a sample of 100 psychological therapy trial protocols registered on the ISRCTN registry (www.isrctn.com). We assessed all protocols as being low- or high-risk via three possible sources of contamination; 1) participant in control arm, 2) participant in intervention arm, 3) therapist in intervention arm.

Results: Overall, we found that the risk of contamination across all 3 sources was low for most studies (86/100 trial protocols; 86%). We identified 14 studies which had a potentially high risk for contamination. The majority of these (N=10) were identified as risk of contamination arising from a therapist in the intervention arm.

Conclusion: The risk of contamination framework we piloted in this study could be a helpful tool for researchers aiming to identify and manage risk of contamination in their trial protocol development. We found that the risk of contamination was relatively low in the psychological therapy trials we sampled for this study, as measured by our framework, and could usually be mitigated through reasonable adjustments to the study design.

Keywords: Clinical Trial; Clinical Trial Protocol; Registries; Research Design; Research Methodology; Psychotherapy

What is new

- **Contamination between intervention and control arms is often a concern in complex intervention trials because participants are often not masked to condition**
- **We developed and tested out a simple framework tool that can be used at the stage of protocol development in clinical trials to assess the risk of contamination**
- **We focused on the plausible routes by which contamination between arms might occur for more realistic risk assessment**
- **We found that risk of contamination was low in 86% of sampled trial protocols, as measured by our tool.**
- **Risk of contamination should be assessed at the protocol development stage of planning a trial, and using this standard framework would improve decision making around any necessary design adjustments required to reduce contamination risk**

Introduction

Complex healthcare interventions have been defined as interventions which are non-standard, have different forms in different contexts, but still conform to specific, theory-driven processes (Hawe, Sheill, & Riley, 2004). Psychological therapies are considered a form of complex intervention due to having several interacting components and processes, which underpin the intervention (Magill, Knight, McCrone, Ismail, & Landau, 2019). The development and evaluation of high-quality complex healthcare interventions is dependent on the use of rigorous research methodology. The Medical Research Council (MRC) (Craig et al., 2008) guidelines for complex intervention development and evaluation state that, wherever possible, it is best practice is to undertake an individually-randomised controlled trial (RCT) design in order to minimise bias. Individual RCTs minimise many forms of bias including selection bias, performance bias, detection bias, and attrition bias (Higgins & Green, 2011), and thus are considered the most robust means of evaluating complex interventions.

Wherever possible, RCTs are designed so that participants do not know whether they are receiving the intervention or the control treatment (often referred to as 'single-blind' in drug trials). However, for psychological therapy trials it is less possible to mask participant allocation as a well-delivered collaborative therapy would involve full disclosure of the type of therapeutic intervention. There may be some ability to mask the intervention if there is an active control, which is the delivery of non-specific therapy factors such as time and attention from an empathic therapist. However, for psychological therapy trials where the control condition is a treatment as usual (TAU) or a waitlist control, participants may be much more likely to be able to accurately discern aware of which arm of the trial they are have been allocated to. Given that masking to treatment allocation is often difficult to achieve in psychological therapy trials for these reasons, a concern that often arises at the design stage is that of how to minimise the risk of contamination. Contamination is the process whereby an intervention intended for members of one arm (the experimental intervention or treatment arm) is received by members of another (the control) (Keogh-Brown et al., 2007). Participants in the control arm could potentially access treatment strategies from the intervention arm due to the intervention comprising transportable components which are difficult to confine (Magill et al., 2019). This can lead to an underestimate of the true effectiveness of the intervention. Using a cluster randomised design is often suggested where the risk of contamination is judged to be considerable. However, cluster randomised designs where groups, rather than individuals, are the unit of randomisation, are not without their drawbacks. Torgerson (2001) has argued that cluster randomised trials usually require much larger sample sizes, making them more expensive and time-consuming, and are susceptible to recruitment bias. It is therefore important to first be sure that contamination is a real, rather than a hypothetical threat, before alternatives to individual randomisation are considered.

Previous studies have shown that contamination rates for complex intervention trials are not insignificant. A large review of complex educational interventions (n=235) found a median level of 24% contamination in participants (Keogh-Brown et al., 2007). Moreover, a recent systematic scoping review of 234 complex mental health intervention studies, identified contamination levels of 13% (of the 10% studies which reported on contamination) (Magill et al., 2019).

Assessing the risk of contamination at the design stage of a psychological therapy trial is challenging. Identifying possible opportunities for contact between participants in the intervention and control arms is not sufficient to indicate a high risk of contamination in of itself. This is because participants simply talking to one another about their therapy does not necessarily constitute contamination, unless it alters the behaviour of those in the control group in some meaningful way. For example, the likelihood of participants being able to pass on psychological skills or strategies learnt within psychological therapy to control participants is unlikely, even when they are sharing a confined treatment environment (e.g. acute mental health inpatient ward). Likelihood of transmission of the so-called 'active ingredients' of a psychological therapy, via therapists or participants in the intervention arm, will depend on several factors, including what the intervention is, and how it is delivered. For example, Magill et al. (2019) identified in their review, that contamination was only a concern when clinicians were delivering treatment in both arms of the trial. It has also been argued that substantial contamination can be tolerated before resorting to a cluster randomised trial, and that contamination can be dealt with appropriately in individual RCT designs, for example, through initial monitoring using a feasibility RCT, consideration of larger sample size and effect sizes (Torgerson, 2001). Other methods for controlling of contamination have included ensuring that clinicians do not offer treatment across multiple trial arms, and informing participants only of the treatment they are receiving.

Choosing appropriate design modifications to minimise any potential risk of contamination therefore includes a broader range of choices for the researcher than simply switching from an individual, to a cluster randomised design. To date however, there is no standard tool which researchers can use at the design stage of a psychological therapy trial to help guide these choices in an informed way. The development and dissemination of such a tool could help researchers make proportionate decisions about how to minimise contamination risk, and to identify where processes are needed to monitor and record any contamination which may occur during the trial (e.g. recording therapy sessions in both intervention and control arm if delivered by the same therapist). Our aim for the current study was therefore to develop a framework to assess potential risk of contamination in psychological therapy trials in mental healthcare, and to pilot it on a sample of protocols from a major trials registry to assess its utility. We also aimed to report on the strategies incorporated into the sample protocols to minimise contamination. Our focus was on assessment of risk at the design phases of a trial (i.e. before a trial starts recruitment), and not assessment of any actual contamination which may have

arisen after completion of the trial, hence the focus on trial protocols, and not reports of completed trials.

Method

Development of framework

Initially, relevant literature was identified which explored the sources of contamination in trials of educational interventions, including a Delphi study of experts' opinion. (Howe, Keogh-Brown, Miles, & Bachmann, 2007; Keogh-Brown et al., 2007)

From this, we identified three main sources of contamination from their findings which would be applicable to mental healthcare trials. These were: A) participant in control arm accesses treatment in the intervention arm themselves; B) participant in intervention arm passes treatment on to participant in control arm; C) therapist providing treatment in intervention arm passes treatment on to participant in control arm. In order to develop the framework, we identified examples of trial design which would exemplify either a high or low risk of contamination via each particular source (see supplementary material for a copy of the framework). For example, for contamination source A, if the treatment in the intervention arm is freely available outside of the trial, such as a commercially available and widely-known therapy app, then a participant in the control group may access it themselves (high risk). However, if the treatment involved a new app which was not yet commercially available, and required a personalised log-in provided by the trial team, then it is unlikely a participant in the control group could access it themselves (low risk). Whilst recognising that a probabilistic risk assessment will always be on a spectrum to some degree from low to high risk, we decided to choose a binary rating scale in order to focus on a broad judgement of balance of probabilities, rather than an arbitrary quantitative rating. We then piloted the framework on a representative sample of psychological trial protocols for mental healthcare trials from a major international trials registry (ISRCTN).

Identification and selection of trial protocols

We identified psychological therapy trial protocols on the ISRCTN registry (isrctn.com), with registration dates (date assigned), under mental and behavioural disorders, in the 24 months from 1st April 2016-31st March 2018. Reasons for exclusion for trials categorised as mental and behavioural disorders, but not meeting criteria for psychological therapy trials as below, were recorded (see supplementary material for criteria).

Data extraction and ratings of protocols

We extracted relevant data from the ISRCTN record. This included general descriptive information about the trial, following the standard headings on the trial registry record (e.g. country of recruitment, recruitment target). Recruitment status and overall trial status (e.g. ongoing or completed) were correct as of date of data extraction (Sep-Nov 2018). We referred to documents linked to the ISRCTN record on the website (e.g. journal paper of protocol, or published results) where they were available if we needed to supplement or clarify information in the trial record.

Where journal articles or other documents were not already linked to the record on the ISRCTN website we did not do a separate search.

We first assessed all trial protocols using the TIDIER tool (Hoffmann, Glasziou, & Boutron, 2014), in order to report how well the intervention was described in the protocol. This was relevant to the aims of the study, as information about how the intervention is delivered, and by whom, affects judgements about risk of contamination (e.g. whether the same or separate therapists are used in the intervention and control arms). In line with the published guidance by Hoffman et al. (2014), we omitted items 10 (modifications during study) and 12 (actual treatment fidelity) of the tool , as we were assessing protocols only, rather than reports of completed trials and these items are not applicable at the protocol stage.

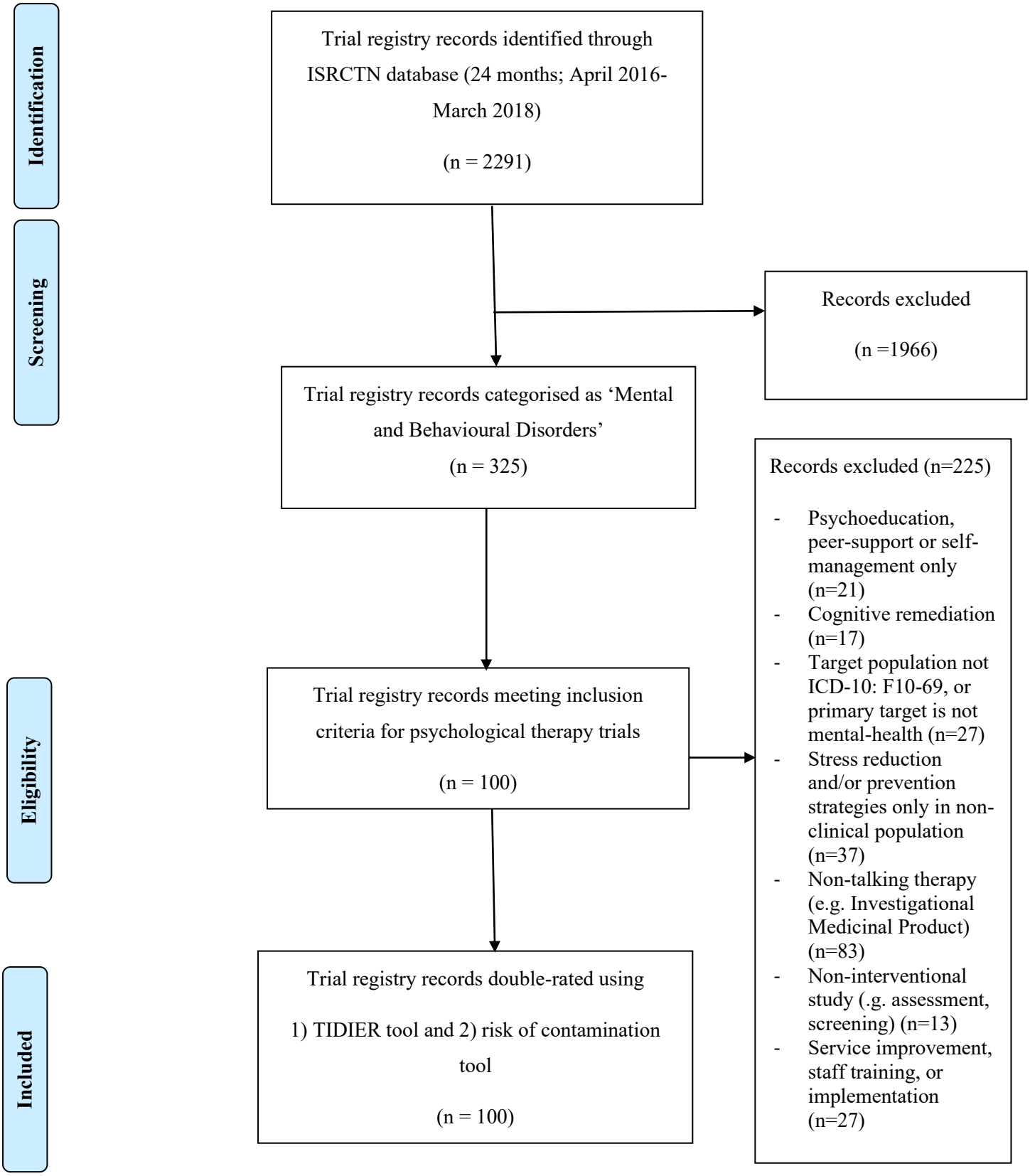
All trial registry records were independently double-rated by the authors PJ and LW, using both the TIDIER tool and the risk of contamination tool developed for this study. Firstly, as part of a calibration and training check we each rated the first 10 records, then cross-referenced and discussed any discrepancies to reach a consensus. We each then went on to independently rate the remaining 90 records, before again cross-referencing and reaching a consensus after discussion on any ratings where there was a discrepancy. For any studies which were identified as a potential high risk of contamination risk under any category (A-participant in control arm, B-participant in intervention aim, C-therapist in intervention arm), we also recorded whether there was any explicit reference to design modifications in the protocol to address any potential risks.

Results

Search results

We found 2291 trial registry records with registration dates between April 2016 and March 2018, 325 of which were categorised under 'Mental and Behavioural Disorders'. The first author (PJ) read the registry record for these 325 studies, and assessed them against the inclusion/exclusion criteria. A total of N=225 studies were excluded at this stage, leaving N=100 studies meeting inclusion criteria as a psychological therapy trial for a mental healthcare condition. These 100 studies went on to be double-rated by both authors as described in the method using 1) TIDIER tool and 2) risk of contamination tool. The search process is shown in Figure 1 as a flow-diagram, following the standard PRISMA diagram used in systematic reviews (Moher, Liberati, Tetzlaff, & Altman, 2009).

Figure 1: Search Results from ISRCTN registry



Characteristics of included studies

Included studies are summarised in Table 1. Approximately half of trials were ongoing (48%), although only a quarter of them were still recruiting (24%). Only half of trials were prospectively registered (51%). The majority of trials were recruiting participants in Europe (82%), were government funded (45%), and recruited adults only (77%). The most common treatment target was mood disorders (27%). Trials were relatively small in size, with almost a third of studies reporting a recruitment target of 50 or less (29%) and only 24% of trials reporting a target of over 200 participants. The majority of trials were individually randomised controlled trials (77%), and used treatment as usual (TAU) as a comparator arm (37%). The most common therapy type was cognitive-behavioural therapy (61%), and was delivered on an individual basis (41%). Although still a minority, we noted that a quarter of studies involved a digital health intervention (25%).

Table 1: Characteristics of included studies

	Frequency (N=100)
Trial Registration	
Prospective	51 (51%)
Retrospective	49 (49%)
Trial Status	
Ongoing	48 (48%)
Completed	52 (52%)
Recruitment Status	
Recruiting	24 (24%)
No longer recruiting	76 (76%)
Continent of Recruitment	
Europe	
- UK	50 (50%)
- Other	32 (32%)
Africa	4 (4%)
Asia	3 (3%)
North America	3 (3%)
South America	2 (2%)
Australasia	2 (2%)
Multiple	4 (4%)
Continent of Study Sponsor	
Europe	
- UK	52 (52%)
- Other	37 (37%)
Africa	0 (0%)
Asia	2 (2%)
North America	5 (5%)
South America	2 (2%)
Australasia	2 (2%)
Participants	
Adults only (18+)	77 (77%)
Children only (<18)	5 (5%)
Both	18 (18%)
Treatment target in ICD-10 categories	
F10-19 (Substance misuse)	13 (13%)

F20-29 (Schizophrenia-spectrum)	11 (11%)
F30-39 (Mood disorder)	27 (27%)
F40-49 (Anxiety disorders)	18 (18%)
F50-59 (Behavioural syndromes)	8 (8%)
F60-69 (Personality disorder)	6 (6%)
No diagnosis	17 (17%)
Recruitment target (across all arms)	
20-50	29 (29%)
51-100	27 (27%)
101-200	20 (20%)
201-500	12 (12%)
>500	12 (12%)
Funder type	
Government	45 (45%)
Research council/organisation	18 (18%)
Charity	15 (15%)
Hospital/Treatment Centre	7 (7%)
University/Education	6 (6%)
Industry	4 (4%)
Investigator Funded	2 (2%)
Professional Society	1 (1%)
Not stated	2 (2%)
Study Design	
Randomised Controlled Trial (RCT)[1]	77 (77%)
Cluster RCT	5 (5%)
Non-randomised controlled trial	1 (1%)
Pilot/feasibility trial (no control group)	11 (11%)
Observational study (no control group)	6 (6%)
Comparator Condition	
Treatment as usual (TAU)[2]	37 (37%)
Active therapy	25 (25%)
Wait-list control	15 (15%)
	6 (6%)

[1] Includes 1 study with a 2nd non-RCT phase (patient preference allocation), and 1 study with 1 RCT site and 1 non-RCT site

[2] Includes 1 study with a control condition described as 'enhanced' TAU

Combination of TAU, wait-list, and active control groups No control group	17 (17%)
Therapy type	
Cognitive-behavioural (including 3rd wave)	61 (61%)
Counselling/Humanistic	6 (6%)
Psychoanalytical/Psychodynamic	2 (2%)
Family/Systemic	2 (2%)
Integrative	3 (3%)
Combination treatments/multiple treatment arms	15 (15%)
No explicit therapy model/therapy model unclear	11 (11%)
Mode of therapy delivery (intervention arm)	
Individual (face to face, phone or combination of both)	41 (41%)
Group Family	20 (20%)
Combination of individual/group/family	3 (3%)
Group workshop with phone/self-help follow-up	9 (9%)
Digital intervention (e.g. web, app, text messages, VR) with some therapist/technician contact	2 (2%)
Digital intervention (e.g. web, app, text messages, VR) with no therapist/technician contact	16 (15%) 9 (9%)

Quality of intervention descriptions

Assessment of studies using the TIDIER tool showed considerable disparity between how well interventions were described between different studies, and between different items on the TIDIER checklist across studies. Results are summarised in Table 2. Areas which were generally described well were the rationale for the therapy, what procedures were involved, in what modality the therapy was delivered, and when and how often the therapy was delivered. However, we found that less than half of studies described any relevant therapy materials (37%), and only 57% of studies described who delivered the therapy. Both of these aspects are important in assessing contamination risk, as they relate to how easily materials may be shared between the intervention and control arm, and whether they may be a risk of contamination arising from the same therapist delivering the therapy in both intervention and control arms of the trial. On a related note, only a quarter (23%) of studies described plans for fidelity assessment, which may mitigate contamination risks, for example if therapy sessions are recorded and assessed for fidelity in the control arm.

Table 2: Summary of TiDIER ratings (N=100)

Checklist Item	Yes Frequency (%)	No Frequency (%)	Unclear Frequency (%)
1: Brief name	48 (48%)	2 (2%)	50 (50%)
2: Why (rationale)	76 (76%)	0 (0%)	24 (24%)
3: What_materials	37 (37%)	31 (31%)	32 (32%)
4: What_procedures	60 (60%)	12 (12%)	28 (28%)
5: Who provided	57 (57%)	13 (13%)	30 (30%)
6: How delivered	95 (95%)	0 (0%)	5 (5%)
7: Where delivered	49 (49%)	37 (37%)	14 (14%)
8: When and how often	75 (75%)	5 (5%)	20 (20%)
9: Tailoring described	58 (58%)	34 (34%)	8 (8%)
11: Fidelity [3]assessment (planned)	23 (23%)	56 (56%)	11 (11%)

[3] Not applicable in N=10 studies where intervention was self-help/digital only with no therapist contact

Risk of contamination ratings

Overall, we found that the risk of contamination across all 3 sources (A-participant in control arm, B-participant in intervention aim, C-therapist in intervention arm) was low for the majority of studies (86/100; 86%). Of the remaining 14 studies, 2 were rated as potentially high risk for contamination source A (participant in control arm), 2 high risk for contamination source B (participant in intervention arm), and 10 high-risk for contamination source C (therapist in intervention arm). No studies were rated as high-risk across more than one possible contamination source (A, B, or C). These 14 studies are further described in Table 3.

Three examples, one for each source of contamination, will be described in this section for illustrative purposes. The Nguvu trial (ISRCTN65771265), which was at high risk of contamination from source A (participant in control arm), involves an intervention delivered in refugee camps in Tanzania, which are organised into 'villages'. There was a potential contamination risk due to control participants being able to access the intervention groups within in refugee camps and the ethical challenges of restricting access to those in the control arm. Therefore, the trial uses a cluster randomised design, so that villages are the unit of randomisation, which means that everyone living in the same village has access to the same intervention (either treatment or control condition). For source B (participant in intervention arm), the PERSUADE trial (ISRCTN23278208) was considered at high risk. This study involved participants attending an initial group workshop, followed by a self-help intervention using a workbook. From the description in the protocol, we were not sure how generic or tailored the workbook, and therefore how easy it would be to pass on the materials and for them to be used meaningfully by a participant allocated to the control condition. Participants were recruited from GP surgeries, so participants from intervention and control arms could conceivably be part of the same social network and have contact with each other. Clustering by GP surgery would be an alternative design, but it was not clear if this had been considered by the research team. The emotion focused therapy and cognitive behavioural therapy trial for treatment of generalised anxiety disorder (ISRCTN52689081) was at high risk of source C contamination (therapist in intervention arm). This trial was going to use the same routine care therapists to deliver both interventions. Risk of contamination was rated as high given the potential for intervention strategies to be delivered in the incorrect arm by the therapists. The authors mitigated against this risk by planning to audio recording all therapy sessions, and for a sample of sessions to be rated by independent raters.

Discussion

This study aimed to develop a framework to identify risk of contamination in psychological therapy trials in mental health care, to inform study protocol development. A framework was developed which examined three key areas of contamination: contamination from participant in control arm accessing the intervention arm themselves, participants in the intervention arm passes treatment on to participant in control arm, and therapist providing treatment in intervention arm passes treatment on to participant in control arm. Application of the framework to 100 trial protocols identified that all possible sources of contamination were captured by the framework, demonstrating its applicability to identifying contamination risk in psychological therapy trial protocols in mental health care. Overall, this framework could be a helpful tool for researchers aiming to identify and manage risk of contamination in their trial protocol development. It should be noted that we only aimed to assess risk of contamination, and this should not be confused with any kind of 'quality assessment' in terms of assessing the protocols. Some studies identified as potentially at risk of contamination could nonetheless be considered high quality, robustly designed studies, with clearly written protocols.

The findings demonstrated that risk of contamination was relatively low across studies and only present in 14% of examined protocols. However, when a high contamination risk was identified, the contamination risk predominantly came from the therapist (10/14; 71%). More specifically, therapists were often described as delivering the intervention across trial arms or having some contact with participants across both arms of the study. A similar finding was identified in a recent study by Magill et al. (2019) who examined complex intervention trials in mental health care. They identified that key areas of contamination related to clinical staff involvement in the trial. This included staff delivering interventions in both arms, clinical staff not delivering the intervention but still treating participants in both arms as part of routine care and therefore learning about the intervention and passing it onto participants, and trial clinical staff communicating between trial arms. This finding demonstrates the importance of incorporating strategies into the study design to minimise this form of contamination. A number of primary protocol papers had explicitly included strategies for managing contamination including, therapists not delivering interventions in multiple arms, and therapists delivering interventions in different arms having no communication about the intervention. It should be noted however, that using the TIDIER tool, only 57% of protocols in our sample had a clear description of who delivered the intervention. We did not automatically categorise a protocol as at high risk of therapist-related contamination when it was not clear who was delivering the intervention. The actual proportion of protocols with a risk of therapist-related contamination may therefore have been higher if we had had full information on who was delivering the intervention in 100% of the sample. However, this limitation would not be applicable to the primary purpose of the framework as a tool to help in the design of trial protocols, as the research team would know who was delivering the intervention, even if they went on to report it inadequately in the trial registry record.

The review identified that cluster randomised control designs were only required when the psychological intervention was widely available or easily transferred between trial arms. This was the case across all contamination categories. For example, in regard to therapist contamination, cluster randomisation was only considered when there was no other means of ensuring that the therapy was delivered by separate clinician across arms, e.g. an intervention being delivered by clinicians in routine care (e.g. ISRCTN38120107). With regards to participant contamination, cluster randomisation was only considered when all participants would potentially have access to the intervention due to it being widely available (e.g. routinely run groups in refugee camps (ISRCTN65771265), or open access online intervention (ISRCTN11086185), or from intervention participants being able to share self-help material (self-help material for refugees in a refugee camp; ISRCTN50148022). We therefore hope that this framework would be helpful in identifying less obvious routes of contamination, which may arise from participants in the trial sharing access to components of the intervention because they come from the same geographic location and/or social network. It is not unknown in these cases for participants in the intervention arm to recommend the trial to others in their network, and encourage others to sign up. Even if the 'new recruits' are subsequently allocated to the control arm, they may still gain access to materials from the intervention arm through their personal contact with existing trial participants. However, we would suggest that cluster randomised control designs are not required when the intervention accessibility is limited and complex to deliver (e.g. a psychological intervention from a highly trained therapist), as this cannot be 'shared' between participants in the same way as a self-help booklet could be. Given the potential drawbacks of implementing a cluster randomised controlled design in terms of sample size and recruitment bias, this suggests that cluster randomisation should only be used when necessary where other methodological adaptation do not mitigate contamination risk. It is important to acknowledge of course, that there may be several valid reasons for choosing a cluster randomised design, other than to protect against contamination (e.g. for interventions which are naturally delivered at cluster level such as in educational settings).

There are a number of strengths to this study. This is the first study, which we are aware, that has developed and implemented a framework to examine contamination risk in psychological therapy trials for mental health care, to inform protocol design. The framework will provide a useful guide to minimise contamination risk in future psychological therapy trials. Moreover, it has been applied to a wide array of psychological therapies demonstrating its broad applicability. We did limit the trial protocols in this sample to a narrow definition of psychological therapy, excluding for example, interventions which consisted of psychoeducation or peer support only. We are not suggesting that the framework would not be relevant to these types of trials, but this would need to be explored in further research. Although we have chosen to focus on the use of the tool for mental healthcare trials for the purposes of this paper, this framework should be equally applicable to other contexts, such as

non-pharmacological interventions in physical healthcare, public healthcare and educational interventions. To examine the framework for its applicability to broader health care interventions, further implementation would be required. As outlined, this framework was devised to be used as a simple tool to inform study protocol development, not a specific guideline; therefore a limitation is that it did not go through the methodologically rigorous process expected for guideline development (Moher, Schulz, Simera, & Altman, 2010). However, the categories of contamination were informed by relevant literature, including a large rigorous study examining contamination in educational interventions (Keogh-Brown et al., 2007).

In conclusion, this framework is a helpful tool in examining contamination risk in psychological therapy trials for mental health care. The framework identified that risk of contamination is relatively low in psychological therapy trials and often can be mitigated again through adjustments to the study design. Cluster, rather than individually randomised controlled trials, are only required to protect against contamination when the intervention is widely available or easily transferrable and not warranted for complex interventions delivered by highly trained therapists.

Author contributions

Pamela Jacobsen: Conceptualization, Methodology, Formal Analysis, Investigation, Data Curation, Writing- Original Draft, Writing – Reviewing & Editing, Project Administration, Funding Acquisition

Lisa Wood: Methodology, Formal Analysis, Investigation, Writing- Original Draft, Writing – Reviewing & Editing

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Declarations of interest

None

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SUPPLEMENTARY MATERIAL

1. **Inclusion/Exclusion Criteria for trial protocols**

2. **Framework for assessing likely risk of contamination in psychological therapy trials**

3. **Table 3: Summary of studies with possible contamination risk (N=14)**

Inclusion Criteria for trial protocols

i. Individual, group or family therapies, delivered in any setting, and via any modality (e.g. face to face, online, telephone).

ii. Therapies aimed at children, adolescents, adults or a mixture.

iii. Therapies aimed at ICD-10 F10-F69 disorders (substance misuse, schizophrenia-spectrum, mood disorders, neurotic disorders, behavioural syndromes (including eating disorders) and personality disorders). Target populations did not necessarily need to meet threshold for diagnosis, have received a formal diagnosis, or be in receipt of mental health services. Interventions aimed at people with physical health conditions, organic disorders, neurodevelopmental or neurodegenerative disorders were included only if they had additional psychological disorders falling into F10-F69 categories (e.g. depression in people with multiple sclerosis).

iv. Any comparator arm (e.g. TAU, active control, other treatment including medication)

v. Feasibility/pilot trials without a control arm (on the basis that a subsequent efficacy trial would likely include a control arm).

Exclusion Criteria for trial protocols

i. Interventions consisting solely of psychoeducation, peer-support, self-management of condition, management of condition via parent/carer, or focused solely on improving parenting/carer skills, which are not part of a broader psychological therapy based on an explicit theoretical model.

ii. Interventions aimed solely at remediation or enhancement of cognitive functioning (e.g. Cognitive Remediation Therapy).

iii. Therapies aimed at ICD-10 disorders outside of F10-69 range, or primary outcome target is not mental-health (e.g. educational attainment, physical activity levels).

iv. Interventions aimed at improving well-being or reducing stress in non-clinical populations (e.g. general public, health-care staff, carers, school children, university students), or aimed solely at prevention of mental health disorders.

v. Interventions consisting solely of an 'Investigational Medicinal Product' (IMP) and/or nontalking therapies or interventions (e.g. arts therapies, acupuncture, exercise).

vi. Non-interventional studies, such as diagnosis, assessment, screening or identification of factors which later predict development of a mental health disorder.

vii. Studies focusing on service improvement, staff training, or implementation only.

Framework for assessing likely risk of contamination in psychological therapy trials

Source of contamination	High-Risk	Low-Risk
Participant in control arm accesses intervention arm treatment via:		
A: Themselves	• **Therapy/intervention is freely available, easy to access outside of trial, and free or low-cost** *(e.g. app available on Appstore/GooglePlay)* • **Hard to gate keep access to therapy/intervention on ethical or practical grounds** *(e.g. therapy groups in communal areas on psychiatric wards)*	• **Therapy/intervention is not widely available, or is prohibitively expensive** *(e.g. long waiting lists for therapy outside of trial context)* • **Trial therapists/research team are sole gate keepers to intervention** *(e.g. new therapy manual/protocol which is not yet used in routine clinical practice)*
B: Participant in intervention arm	• **Therapy/intervention is single-faceted, easily passed on, and not individually tailored** *(e.g. psycho-educational leaflet)* • **No specific skills or training required to deliver intervention** *(e.g. self-help booklet)*	• **Therapy/intervention is multi-faceted, cannot be easily passed on, and is individually tailored** *(e.g. CBT based on idiosyncratic psychological formulation)* • **High degree of skills and training required to deliver intervention** *(e.g. trial therapists have established competencies in intervention they are delivering)*
C: Therapist who is providing treatment in intervention arm	• **Intervention consists of training therapist in a new skill which cannot be unlearnt/easily switched off** *(e.g. training in compassionate communication style)* **Same therapist in intervention/control arm** *(e.g. single therapist trial)*	• **Intervention consists of discrete components which can be delivered according to a standard manual/protocol** *(e.g. use of behavioural experiments in CBT for anxiety)* **Separate therapists for intervention/control arm, or minimal overlap in staff working with participants in both arms of the trial** *(e.g. trial therapists deliver intervention, routine clinical staff deliver TAU)*

Table 3: Summary of studies with possible contamination risk (N=14)

Contamination Source	Registration Number	Title	Study Design	Adaptations to study design to mitigate risk of contamination	Comments
A: Participant themselves	ISRCTN65771265	1. Nguvu: Evaluating an integrated approach to reduce intimate partner violence and psychological distress in refugees in Tanzania	Cluster RCT	Cluster randomised design	Intervention is designed to be provided in refugee camps, via pre-existing women's groups across different villages. Trial protocol notes that it would not be ethical or practical to try and exclude women who had been allocated to the control arm, from accessing groups within the same village for participants in the intervention arm, if the trial was designed with individual participant randomisation. Therefore the village is the unit of randomisation (village=cluster). Separate caseworkers deliver intervention and treatment as usual (TAU) across the different villages.
	ISRCTN11086185	2. CANreduce 2.0 - comparing two differently optimized versions of a web-based self-help program to reduce	RCT	Multiple registrations from same IP address are blocked	Study compares 2 forms of web-based intervention (enhanced with unenhanced) with a wait-list control. A participant allocated to the control group could possibly try and re-register to get access to the intervention programme, but this risk has been addressed in the protocol by blocking multiple

		cannabis use with each other and a waiting list			attempts from the same IP address. Each participant receives a personal log-in and people can work through modules in their own time and order, so risk of contamination by participant in the treatment arm is low, as the intervention is not easily shared. Response to e-mail queries is only available in 1 arm of trial, so there is no risk of contamination from the therapist.
B: Participant in intervention arm	ISRCTN50148022	3. Self-help plus (SH+) for South Sudanese refugees in Uganda	Cluster RCT	Cluster randomised design	Intervention is based on self-help delivery within a refugee camp, so materials could easily be shared by participants in the intervention arm, with participants in the control arm, if they were within the same refugee camp. Therefore the village is the unit of randomisation (village=cluster), so participants in the intervention arm do not have close contact with people allocated to the control arm.
	ISRCTN23278208	4. Preventing depression study: PERSUADE	RCT	None noted in protocol	Participants attend an initial group workshop (8 hours over 1-2 days), then are given a self-help workbook to use (expected time commitment not stated). It is not clear from the protocol how tailored/generic the workbook is, and therefore, how feasible it would be for participants in the treatment arm to share it with a participant in the control arm (TIDIER item 3). Contact between participants in intervention and

					control arms could be possible as participants are recruited through GP surgeries, and people from the same family or belonging to the same social networks may be registered at the same GP practice as one another.
C: Therapist in Intervention Arm	ISRCTN40388402	5. Violence and alcohol abuse intervention for Swedish youth – evaluation for evidence-based practice	RCT	None noted in protocol	It is not possible to determine from the trial protocol whether staff (social worker/midwife) involved in delivering the intervention arm treatment also have contact with participants in the control group. This is important as staff training in the intervention (motivational interviewing; MI) could possibly lead to these techniques or skills being used by the same staff during standard contacts with participants in the control group. There is no reference to recording sessions in the control arm, which could help detect any contamination should it arise.
	ISRCTN16382776	8. Mindfulness Based Cognitive Therapy (MBCT) programme for depression in people with early stages of dementia	RCT	None noted in protocol	There are no details in the trial protocol about who delivers the intervention (TIDIER item 5). If routine clinical staff were recruited and trained to deliver the intervention, it is possible they might start to introduce mindfulness exercises in other clinical contact they have with control group. This would not a be a concern if the MBCT intervention was delivered by

					separate trial therapists, who were not part of the routine clinical team, or if a cluster randomised design was used. However, the MBCT intervention is a complex intervention, comprising several components, and so access to isolated components by participants in the control group (e.g. mindfulness practises, but without teacher-led enquiry) may not in themselves be seen to be a significant contamination threat.
	ISRCTN77037777	9. A study to explore whether a multi-component psychosocial intervention can reduce substance use in adolescents who are involved in the criminal justice system in the UK	RCT	None noted in protocol	The trial protocol states that the intervention is delivered by youth workers trained in motivational interviewing (MI), who are then given extra training in the trial intervention (RISKIT-CJS). RISKIT-CJS is described as a multi-component psychosocial intervention designed to reduce substance misuse in adolescents who are involved in the criminal justice system in the UK. The CBT components include MI, psycho-education, anger management, assertiveness training, mindfulness, & planning for the future. It is not clear whether youth workers delivering the intervention in the treatment arm might have contact with participants in the control arm, if they were service users of the same youth offending team. If so,

					there could be the potential for contamination arising from youth workers providing aspects of the intervention to participants in the control group. A cluster-randomised design might be a possible solution to this.
	ISRCTN12077707	10. DECRYPT: Delivery of cognitive therapy for young people after trauma	RCT	No contact between clinicians delivering therapy in treatment arm and participants in the control group	Possible risk of therapist contamination given pragmatic trial design (routine clinicians deliver the therapy in the intervention arm). This possible risk is specifically addressed in the protocol however, as it states that there would be no contact between clinicians delivering the trial therapy, and participants in the control group (who just receive TAU).
	ISRCTN60291091	11. Brief interventions to reduce risky drinking in parents of children referred to children's social care	Cluster RCT	Cluster randomised design	The unit of randomisation is the social care practitioner, as a single practitioner works with all family members (this will prevent within family contamination). Practitioners in the control group receive no extra training in the intervention from the treatment arm of the trial (alcohol intervention).
	ISRCTN17852603	12. Mindfulness for paranoia	RCT	None stated in protocol	It is not clear in the trial protocol exactly who delivers the intervention (TIDIER item 5). The protocol refers to 2 therapists, but it is not made explicit whether these

					are clinicians involved in providing routine clinical care, who might also have contact with participants in the control group. This would not a be a concern if the mindfulness groups were delivered by separate trial therapists, who were not part of the routine clinical team, or if a cluster randomised design was used. However, the intervention is a complex intervention, comprising several components, and so access to isolated components by participants in the control group (e.g. mindfulness practises, but without teacher-led enquiry) may not in themselves be seen to be a significant contamination threat.
	ISRCTN12268776	13. A study of Acceptance and Commitment Therapy for older people with chronic worry who have not responded to treatment	Pilot/feasibility trial (with no control group)	N/A - current study does not have a control group	If the pilot trial was successful, and led onto a future RCT, there could be a potential risk of contamination if the therapists providing the intervention also had contact with, or provided care for, participants in the control group. The potential contamination risk would also depend on what the control arm was, i.e. whether it was TAU or an active therapy control.
	ISRCTN38129107	14. The coaching for smokers trial	Cluster RCT	Cluster randomised design	The unit of randomisation is the GP, who receives extra training and delivers the intervention. The trial protocol notes that a cluster randomisation design is

					required, as it may be difficult for GPs to switch between the control/treatment approaches between different patients.
	ISRCTN52689081	15. A comparison of emotion-focused therapy and cognitive-behavioural therapy in the treatment of generalised anxiety disorder	RCT	Fidelity checks in both arms of the trial (therapy sessions are audio-taped)	As the same routine care therapists provide therapy in both arms of the trial, there is a possibility of contamination by the therapist, but the trial protocol notes there are plans in place to check treatment fidelity in both arms of the trial. Sessions are audio-recorded for fidelity checks, and a sample of sessions from all therapists are rated by at least 2 independent raters.
	ISRCTN55239132	16. Evaluation of Eye Movement Desensitization and Reprocessing (EMDR) and Retrieval only Condition for Posttraumatic Stress Symptoms on Physiological Markers	RCT	None stated in protocol	The main difference between the therapies in the intervention and control arms is whether eye movements are used. The trial protocol does not describe who delivers the intervention (TIDIER item 5). If the same therapists deliver treatment in both arms of the trial, it is possible that eye movements could be delivered accidentally in the control arm. The trial protocol does not mention any plans for fidelity checks (TIDIER item 11), which could help provide data on whether any actual contamination occurred in the control group.