What should we report? Lessons learnt from the development and implementation of serious adverse event reporting procedures in non-pharmacological trials in palliative care

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Abstract

Background/aims: Serious adverse event reporting guidelines have largely been developed for pharmaceutical trials. There is evidence that serious adverse events, such as psychological distress, can also occur in non-pharmacological trials. Managing serious adverse event reporting and monitoring in palliative care non-pharmacological trials can be particularly challenging. This is because patients living with advanced malignant or non-malignant disease have a high risk of hospitalisation and/or death as a result of progression of their disease rather than due to the trial intervention or procedures. This paper presents a number of recommendations for managing serious adverse event reporting that are drawn from two palliative care non-pharmacological trials.

Methods: The recommendations were iteratively developed across a number of exemplar trials. This included examining national and international safety reporting guidance, reviewing serious adverse event reporting procedures from other pharmacological and non-pharmacological trials, a review of the literature and collaboration between the ACTION study team and Data Safety Monitoring Committee. These two groups included expertise in oncology, palliative care, statistics and medical ethics and this collaboration led to the development of serious adverse event reporting procedures.

Results: The recommendations included; allowing adequate time at the study planning stage to develop serious adverse event reporting procedures, especially in multi-national studies or research naïve settings; reviewing the level of trial oversight required; defining what a serious adverse event is in your trial based on your study population; development and implementation of standard operating procedures and training; refining the reporting procedures during the trial if necessary and publishing serious adverse events in findings papers.

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Background

More research is needed in palliative care to improve the evidence base that underpins clinical practice [1], especially as the need for palliative care is predicted to increase substantially by 2060 [2]. There is a commensurate need to increase the number of high quality trials in palliative care as they are an optimal design for testing the effectiveness of treatments and therapeutic interventions [3, 4]. Many interventions and treatments commonly used in palliative care have little supporting trial evidence [5]. Clinical trials, as well as testing effectiveness, also need to assess whether the novel treatment or intervention is in fact safe [6].

Safety reporting procedures aim to capture any adverse events that may arise during a trial [7]. Trial protocols should contain details of how adverse events are to be identified, collected, assessed, reported and managed [8]. Findings papers should also report on the adverse events that have occurred during a trial [7, 9, 10]. There are internationally agreed definitions and reporting procedures for pharmacological trials [11]. In a clinical trial, an adverse event is any untoward medical occurrence that is experienced by a trial participant which is not necessarily related to the intervention [12]. The adverse event is classified as serious when, at any dose, it results in: death, is life-threatening, requires inpatient hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability/incapacity or is a congenital anomaly/birth defect [12].

Monitoring of adverse events during a trial is key to ensuring patient safety but structures and processes, including nomenclature, can vary depending on the funder, trial type and jurisdiction [13]. Generally, an internal study team or group is responsible for the day to day running of the trial while a Trial Steering Committee, made up of largely independent members including patient representation, provides additional scrutiny [13]. An independent Data Safety Monitoring Committee may also be set up, more commonly in pharmaceutical trials, to monitor un-blinded safety and efficacy data and if required recommend the trial is stopped to safeguard the interests of participants [13, 14]. Ethical approval processes can vary internationally [15] but a research ethics committee’s role is to review the potential risks of a study [11]. Requirements for reporting adverse events to research ethics committees can vary between nations [16] but international guidance recommends that unexpected serious adverse events related to the intervention (SUSARs) be promptly reported [11].

There is evidence that serious adverse events, such as psychological distress, can occur in non-pharmacological trials [17]. This paper focuses on serious adverse event reporting in palliative care non-pharmacological trials as there is a lack of guidance for researchers. This is also an issue outside palliative care. One review of psychological trials highlighted an over reliance on the definition used in pharmacological trials and that researchers did not identify which serious adverse events might likely arise from a specific intervention in a particular population [18].

The definition of a palliative care population can vary [19, 20] but in this paper a palliative care trial focuses on those patients living with advanced malignant or non-malignant disease and their family carers. This group of patients are viewed as vulnerable as they have complex physical, psychosocial and spiritual needs and can have a limited life expectancy [21]. They are cared for in diverse clinical settings and receive care from specialist and/or generalist palliative care professionals. Non-pharmacological palliative care interventions are heterogeneous. Typically, they are complex interventions that reflect a holistic and multi-disciplinary approach to care [22] with quality of life and/or symptom control being the primary outcome [22–24] rather than survival or disease response [25]. Interventions may be taken from other patient populations and applied to those living with advanced disease [26] or developed specifically to meet the needs of this patient group [27]. The characteristics of a non-pharmacological palliative care trial make implementing serious adverse event reporting procedures challenging.

The challenges of applying the standard serious adverse event definitions and reporting procedures was considered in two recent palliative care non-pharmacological trials. The ACTION study was a cluster randomised controlled trial assessing the effects of an advance care planning programme on the quality of life of patients with advanced lung or colorectal cancer. The
Review level of trial oversight required (see Fig. 1).

Factored in adequate time at the study planning stage to develop trial reporting procedures in palliative care non-pharmacological trials. Table 1

| Recommendations for managing serious adverse event reporting procedures for the ACTION trial |
|---|
| - Factor in adequate time at the study planning stage to develop serious adverse event reporting procedures especially in a multinational study or for research naive settings such as a nursing home. |
| - Review level of trial oversight required (see Fig. 1). |
| - Define what a serious adverse event is in your trial, based on your study population, including their health state, the expected risks and the type of events that should be reported.  |
| - Develop documentation to support serious adverse event reporting. |
| - Implement serious adverse event reporting procedures. |
| - Monitor serious adverse events during the trial. |
| - Refine the reporting procedures during the trial if necessary. |
| - Report the serious adverse events that occur during the trial in the final report papers. |

During the trial, a review of the literature was carried out to explore how the serious adverse event reporting procedures of the ACTION study compared with other trials of palliative care psychological interventions (see Additional file 1). The review highlighted that there is a lack of evidence of how serious adverse events should be monitored in these type of studies. How the study teams planned to manage psychological distress and deal with concerns raised from questionnaire responses were sometimes reported in the published trial protocols. There was also a lack of reporting of serious adverse events in the final reports of included studies which could suggest that no serious adverse events have occurred, they were not recognised or recorded or they were recorded but not reported [18].

The recommendations outlined below were iteratively developed from the learning across both trials.

The recommendations

Experience from both trials highlighted the need to factor in adequate time at the study planning stage to develop serious adverse event reporting procedures that reflected the study population, the intervention being tested and that aligned with international, national and local procedures. The Namaste trial also required additional time as the nursing home sites had not taken part in a previous trial and for some of the homes, this was their first experience of research.

Defining what a serious adverse event is in your trial

The importance of defining what a serious adverse event is in your trial based on your study population was...
identified. This definition should take account of their health status, the expected risks and the type of events that should be reported. How this process was operationalised in the two trials is described in Table 2. In the Namaste trial, patient and public involvement representatives provided advice on the wording of participation information [34] and questionnaires to try and reduce the risk of distress.

**Documentation to support serious adverse event reporting**

Serious adverse event standard operating procedures and reporting forms were developed for both trials. The Clinical Trial Unit that was managing the Namaste trial data had limited experience of supporting non-pharmaceutical trials. Their standard reporting procedures had to be adapted to fit the trial design and clinical setting which added additional time to the study set up process. In the ACTION trial, a form for documenting routine hospital admissions was produced that asked for reason and length of admission. In both trials, a form was created to document all deaths which included the date and cause of death, in the ACTION trial place of death was also documented.

**Implementation of serious adverse event reporting procedures**

In the ACTION trial, oncologists and research nurses were experienced in pharmacological trial serious adverse event reporting procedures but less so in non-pharmaceutical studies. Informal training was provided at the start of study and support was available throughout the trial and if a serious adverse event was suspected. In the Namaste trial, nursing home staff were unsurprisingly largely research naïve so a research manual was developed to explain reporting procedures to non-research staff. Formal research training was provided at the start of the study and support was available throughout the trial and if a serious adverse event was suspected.

**Monitoring of serious adverse events during the trial**

Multiple strategies were used to monitor serious adverse events in both trials and reporting procedures were refined during the trial as necessary (see Table 3). As recommended by the Consort guidelines [7], both passive and active surveillance strategies were used. Passive surveillance involved the recording of spontaneously reported serious adverse events by patients, their proxies or health care professionals. In the ACTION trial, active surveillance involved the review, by the Data Safety Monitoring Committee, of the total number of patients screened for eligibility, who was eligible, asked for consent, and included plus response rates per study arm and per tumour type, the primary outcome measure and hospital admission and death data in both arms of the trial. In the Namaste trial, a review of baseline questionnaires highlighted the need to monitor patient pain scores and guidance for highlighting concerns to the nursing home manager was developed.

**Reporting of the serious adverse events that occur during the trial**

The serious adverse events that occurred were reported in the final report papers. In the ACTION trial, three serious adverse events related to the intervention were
Table 3 Monitoring of serious adverse events during the trial

| ACTION trial                                                                 | Namaste trial                                                                 |
|------------------------------------------------------------------------------|-------------------------------------------------------------------------------|
| Regular telephone and face to face contact with clinical sites.               | Regular telephone and face to face contact with nursing home sites.            |
| Data Safety Monitoring Committee review of:                                   | Review of serious adverse event forms by study coordinating centre and findings reported to the Trial Steering Committee. |
| • Serious adverse event forms                                                 | Monitoring of pain scores reported during the trial.                           |
| • Items from the Quality of Life questionnaires related to distress           | Study coordinating staff to report concerns to nursing home manager if pain scores high. |
| • Routine hospital admission and expected death information                   |                                                                                |
| • Total number of patients screened for eligibility, who were eligible, asked for consent, and included plus response rates per study arm and per tumour type |                                                                                |
| Liaison with clinical staff, as necessary, to ensure an appropriate plan of care was put into place. |                                                                                |

Discussion

The need to improve the quality of reporting of serious adverse events in trials has been recognised [7, 9] but there is a lack of practical guidance on how to manage this process, particularly in palliative care non-pharmacological trials. This may be because published trial protocols and results papers may have limited space to document these processes and/or they are challenging to implement because of the characteristics of a palliative care trial. This paper addresses this issue by presenting a number of recommendations based on the lessons learnt from managing serious adverse event reporting procedures in two non-pharmacological trials in palliative care.

When designing a palliative care non-pharmacological trial the possibility that serious adverse events may occur should be not be dismissed and should be actively considered, including ‘worst case scenarios’. In pharmaceutical trials, the potential for serious adverse events to occur is evaluated in four phases of trial development. Phase I trials, historically referred to as ‘toxicity trials’, test a new drug in a small number of participants to identify the dose range and the drug’s safety profile [16, 37]. Phase II trials evaluate safety in a larger group of participants and set the dosage schedule for further phases. Phase III trials are usually double blind randomised controlled trials involving more participants and they assess efficacy and serious adverse events between intervention and control arms. Phase IV studies are post marketing studies and evaluate serious adverse events related to longer term use [16, 38]. The four stages of the Medical Research Council framework for developing complex interventions reflect the phases of drug development [39, 40]. As discussed previously, palliative care non-pharmaceutical trials typically involve complex interventions. The potential for serious adverse events to occur is something that should be explicitly explored earlier in their development and conduct. For example, in the feasibility/piloting stage, one of the trial’s objectives should be to determine the type and consequences of any serious adverse events related to the intervention or study procedures prior to a definitive trial [41]. Reviews of feasibility/pilot studies, however, show that this is not always the case [42, 43].

This paper also contributes to the discussion regarding trial safety oversight in the context of palliative care non-pharmaceutical trials. Setting up a Data Safety Monitoring Committee or Trial Steering Committee with appropriate expertise can be time consuming, an issue also raised in the general trial literature [44]. This can be more challenging for international studies when there may be a number of different local regulatory requirements to incorporate into the process. The criteria for determining the need for a Data Safety Monitoring Committee are not well defined, even in pharmaceutical trials [44]. Research ethics committees, as in pharmaceutical trials, should review whether potential serious adverse events have been considered and how they are going to be monitored in these type of studies [11].

The MORECare recommendations for evaluating complex interventions in end of life care do not cover serious adverse event reporting or how safety should be monitored in this context, including the role of ethics committees and other monitoring committees [5]. This is an area of palliative care trial methodology that requires further research. In this context, a risk assessment matrix may help researchers determine the type of oversight committee required for their trial (see Fig. 1) but this requires further research. In the palliative care context, risks associated with introducing the trial may also need to be considered, as this will be dependent on the patient’s level of awareness and the communication skills of the recruiter [45].

Conclusions

There may be a greater level of risk associated with pharmaceutical trials but as our experience has
highlighted non-pharmaceutical trials are not, as is sometimes assumed, risk free. There is a need for those involved in non-pharmaceutical trials to share their experiences of managing this challenging aspect of trial conduct. This will ensure the procedures for managing serious adverse events are continually refined and improved so optimising patient safety, with further research warranted.

**Supplementary Information**

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**Authors’ contributions**

LD led the writing of the paper while all the other authors contributed to revising the manuscript. LD and DCM carried out the review. All authors reviewed and approved the final draft.

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**Availability of data and materials**

All data generated or analysed during this study are included in this published article and its supplementary information files. In addition, the ACTION and Namaste trial protocol and findings papers are open access.

**Ethics approval and consent to participate**

Research Ethics Committee approval was obtained in all six countries taking part in the ACTION study (NRES Committee North West - Liverpool East 14/...
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