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Patient Reported Outcome Alerts: Ethical and Logistical Considerations in Clinical trials.

**Authorship**

Derek Kyte, MSc1, Heather Draper2;3, PhD Melanie Calvert, PhD1;3\*

**Affiliations**

**1**Primary Care and Clinical Sciences, University of Birmingham, Birmingham, UK,2Medicine, Ethics, Society and History**,** University of Birmingham, Birmingham, UK, 3MRC Midland Hub for Trials Methodology Research, UK

\* Corresponding author: Melanie Calvert

 Contact details:

School of Health and Population Sciences

University of Birmingham

Edgbaston

Birmingham  B15 2TT

UK

Tel:  +44 (0) 121 414 8595

Fax:  +44 (0)121 414 3353

Email: M.Calvert@bham.ac.uk

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Investigators and institutional review boards (IRBs) are increasingly concerned about the risks to patients, and the potential legal liability, when patient-reported outcome (PRO) information is not clinically reviewed to detect PRO ‘alerts’, that is, concerning levels of psychological distress or physical symptoms that may require an immediate response.[1](#_ENREF_1) PRO alerts may present as extreme scores on questionnaire’s, or in unprompted additional information recorded by the participant on the PRO, which is subsequently viewed by research personnel.

Even when such alerts are discovered during a trial, for example by research personnel who may be reviewing the PRO questionnaire for missing items, there is no clear consensus in the literature or among IRBs about how alerts should be managed. Further, there is a general lack of management guidance in trial protocols and training.[2](#_ENREF_2) This may lead to suboptimal patient care, but may also lead to variations between sites in the management of symptoms that could affect study results. Evidence suggests, in the absence of appropriate guidance, researchers responding to an alert may administer unspecified interventions to aid the trial participant; such interventions may go unreported.[2](#_ENREF_2) If the primary outcome of a trial is influenced by participant distress captured by the trial PRO, and such distress is not routinely discovered and managed in clinical practice, ad-hoc interventions may result in co-intervention bias, i.e. bias caused by ‘any intervention other than the experimental maneuver that alters the frequency of a trial’s outcome of interest’.[3](#_ENREF_3)

Accordingly, trial management groups should acknowledge the potential implications of PRO alerts in their study from its outset, and have an *a priori* plan for consistent/standardized management of alerts that is clearly communicated to all appropriate trial staff. The optimal content of such a plan is unclear. There are at least four options, each with their own advantages and disadvantages (table 1).

In some trials, research personnel are simply instructed not to view completed PRO questionnaires. The ethics of such an approach are questionable. Researchers have a duty of care to protect the interests of patients in a trial and the decision to blind research personnel to PRO data may lead to patients with manageable symptoms receiving suboptimal care. Furthermore, blinding would hinder active real-time monitoring of questionnaire completion, thereby reducing data quality.

In other trials, research personnel are instructed to check questionnaires to ensure items have not been missed inadvertently[4](#_ENREF_4), having first issued participants with a two-part disclaimer at enrollment, indicating: (1) that the PRO data they provide will not be used to inform their clinical care, and (2) if study participants have concerns they should contact their usual Physician for advice. This option has few costs, dissuades participants from tailoring their responses in the belief they might influence their care, lessens the burden on researchers by providing clear guidance, and regards study participants as autonomous and responsible, able to identify their own needs and respond accordingly. This approach, however, assumes that study participants have the skills and insight to identify if and when they need help, and thus arguably constitutes an abdication of responsibility for those that do not. Furthermore, this option does not allow trialists to formally assess levels of co-intervention.

A third alternative is for researchers to retain the first part of the above disclaimer, but also provide an in-house 24-hour helpline service (or the contact details of an independent professional helpline). This permits researchers to discharge their obligation to protect participants by ensuring the availability of personalized advice. The onus, however, again rests with the patient to self-refer, which may not be a viable option for all trial cohorts. An ‘in-house’ service need not be provided with anonymity. It may, therefore, enable researchers to collect alert-related intervention data, ideally using a mechanism to follow up participants, so all subsequent co-interventions can be captured. The advantage of a helpline option is it provides an immediate response to need. Not all trials review or input PROs as they are received, which could result in a delay in patients receiving care if they have to wait for the researchers to notice they may require assistance. One notable disadvantage of a trial helpline is its resource implications.

A fourth option is for trials to implement real-time review and notification of PRO alerts for selected items or severities (e.g. suicidal thoughts or severe depression).[5](#_ENREF_5) Here, research personnel could be directed to routinely screen questionnaires and initiate a first response if scores reach a pre-defined threshold. Alternatively PRO data entry could trigger an alert on a computer screen. An appropriate trial response would require that a pre-specified tailored action plan be included in the protocol, reinforced by supporting trial documentation and training. For most trials, a sensible first step might be to contact the study participant directly to discuss the result. This would help account for potential PRO measurement error, as a clinician could evaluate the concern with the participant directly and offer advice accordingly. Participants would need to understand how their PRO data might be used in these circumstances, as returns could not be anonymous. A disadvantage of this approach is that it may undermine participant privacy and lead to unwelcome offers of help, and may influence the way patient’s self-report trial outcomes. Active PRO alert monitoring commits researchers to the timely entry of PRO data into a system that is capable of triggering an alert, which may add substantially to research infrastructure and costs. It does, however, enable data on co-interventions to be collected (assuming appropriate mechanisms are in place), and does not depend on patients having insight into the extent of their problems. Rather, it places the onus on researchers to fulfill their obligation to protect study participants’ interests, particularly once the researchers know that these interests may have been compromised.

There are strong ethical and scientific reasons to reach consensus about how PRO alerts should be dealt with by researchers. Ad-hoc interventions may leave participants at risk of harm, place strain on individual researchers, risk co-intervention bias and compromise the integrity of study. The appropriate management strategy is unclear at this stage – the correct response may depend on the nature of the trial and its risk profile. Even if inter-trial consistency is not appropriate there should at least be consistency across sites within trials. Researchers must, therefore, recognize that PRO alerts are a possibility that should be accommodated at the design stage of the study. Finally, arrangements set out in the protocol need to be reinforced by IRBs, with clear information for both participants and researchers.

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Table 1 – Potential approaches to PRO alert management

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| --- |
| Summary of approaches to PRO alert management |
| **Approach** | **Trial Level Considerations** | **Participant Level Considerations** |
| *Research personnel blinded to PRO data* | * Simple to implement, low cost
* Hinders monitoring/prevention of missing data by research staff
* No capacity to capture data on co-interventions
 | * Ethically questionable, trial participants ‘in need’ may receive sub-optimal care
 |
| *2-part disclaimer* | * Low cost - no alert monitoring resources required
* Allows monitoring/prevention of missing data by research nurses
* Potentially lessens burden on research staff
* Dissuades patient from tailoring questionnaire responses to influence care
* No capacity to capture data on co-interventions
 | * Requires participant to identify their own needs and respond accordingly if they require assistance
* Participant may lack insight or frame of reference to determine if their problem warrants intervention
 |
| *24-Hour Helpline* |  * Allows monitoring/prevention of missing data by research nurses
* Discharges researcher obligation to protect trial participants by ensuring availability of personalized advice
* Ability to capture data on co-interventions (in-house helpline only)
* Helpline staff require suitable training and support
* Resource implications
 | * Immediate response available
* Requires participant to identify their own needs and respond accordingly
* Participant may lack frame of reference to determine if their problem warrants intervention
 |
| *Active PRO alert monitoring* | * Allows monitoring/prevention of missing data by research personnel
* Satisfies researcher obligation to protect trial participants
* Ability to capture data on co-interventions
* Requires pre-defined thresholds for alert generation
* Requires pre-specified tailored response list/action plan and timely entry of PRO data into trial systems
* Research staff require suitable training and support
* Resource implications
 | * Does not depend on participants having insight into the extent of their problems
 |

Abbreviation: PRO, patient-reported outcome.