



Short communication

Considerations for unblinding individual study participants during vaccine trials



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ABSTRACT

Premature unblinding of individual participants is rarely reported in publications, but such unblinding can disrupt vaccine trials by causing worry and drop-out of other participants or “pseudo unblinding,” in which participants or investigators over-interpret certain symptoms as being related to receiving an investigational product. This review summarizes appropriate reasons for unblinding in vaccine trials. Regulatory guidance could be improved by distinguishing guidance for vaccine trials from drug trials, with the recognition that unblinding individual participants in vaccine studies is rarely needed for management of adverse events following immunization.

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1. Background

Randomized, double-blind clinical trials provide the least biased assessment of the safety and efficacy of biologic products. [1–4] The extent to which individual participants are unblinded

during trials and the impact on study conclusions are generally not reported in formal publications of clinical trials, contributing to the underappreciation of problems associated with unblinding. [5,6] In our experience, there has been considerable variability in the criteria used for unblinding individual participants in vaccine trials. The purpose of this review is to summarize situations in which premature unblinding of individuals has occurred in recent vaccine trials and to offer considerations for when this should be

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done. Issues regarding unblinding of all participants when study endpoints have been reached are not the focus of this limited review.[7]

The authors have extensive collective experience in conducting and overseeing clinical trials; participating in Data and Safety Monitoring Boards (DSMBs), Safety Monitoring Committees (SMCs), and Institutional Review Boards (IRBs); as well as reviewing manuscripts on clinical vaccine trials. The authors are currently participating in the Safety Platform for Emergency vACCines (SPEAC) meta-DSMB that provides safety oversight of trials funded by the Coalition for Epidemic Preparedness Innovations (CEPI).[8] This limited review of unblinding is based upon our accumulated experience, knowledge of clinical trials and regulatory guidelines, a limited review of the literature, and responses to a standard survey distributed to seven experts external to the SPEAC meta-DSMB (see acknowledgments). These experts have extensive experience conducting or overseeing trials, including recent COVID-19 vaccine clinical trials. Structured one-hour interviews were conducted based on standardized questions (Supplemental table) distributed beforehand regarding experiences with unblinding individual study participants. The external experts were informed that their experiences and opinions would not be attributed to them to avoid concerns regarding conflicts with their respective organizations.

2. Regulatory guidance

The International Council for Harmonisation (ICH) guidelines provide unified standards for clinical trials in the European Union (EU), Japan, and the United States. ICH E6 Guideline for Good Clinical Practice (GCP)[9] calls for the ability to rapidly unblind individuals with serious adverse events. More specific information is provided in the Question and Answer section of the EU Clinical Trial Regulation including “Unblinded information should only be accessible to those who need to be involved in the safety evaluation and regulatory reporting. A separate procedure should exist for SARs (Serious Adverse Reactions) unblinded for emergency purposes for the clinical management of SARs by the investigator.”[10] Seasoned investigators and regulatory authorities generally agree that unblinding individual subjects should be considered only when knowledge of the treatment assignment is essential for the subject’s clinical care.[7,11]

Some challenges occur in vaccine trials because most regulatory guidance documents do not differentiate between drug and vaccine trials. In contrast to drug trials, knowledge of the vaccine administered is rarely essential to provide immediate care for study participants with adverse events. Treatment in most instances is the same whether the investigational vaccine, comparator vaccine or placebo is administered, particularly if the vaccine is delivered as a single dose. However, clinicians caring for study participants often want to know what the affected patient received to identify potential causes for an adverse event. Too often they assume that an investigational vaccine is the cause of an adverse event, and they do not conduct the needed studies to exclude likely alternative known causes. An example would be searching for *Campylobacter* infections in patients with Guillain-Barré Syndrome following vaccination.[12,13] For most adverse events of special interest (AESI) there are no specific tests that can implicate a vaccine as a cause. Some trials have been paused to allow for careful investigation of the adverse event to confirm the diagnosis and/or conduct studies looking for possible alternative causes. On some occasions, sponsors or investigators have requested unblinding individual trial participants because of concerns regarding criticism and/or legal liability for not unblinding. Also, investigators or sponsors have unblinded participants with an AESI in the hope of avoiding the need to pause the trial if the

participant had received the placebo. However, if the background rates of the serious adverse event in the population have not been exceeded, pausing may not be indicated.[14] Rates can usually be estimated for most adverse events even if rates for the specific country where the trial is being conducted are not available.

Examples of appropriate, but rare, reasons for unblinding individual participants during vaccine trials:

1. Anaphylaxis. Although the immediate clinical management of serious allergic reactions is similar regardless of the cause,[15] a study participant may have a future need for other vaccines with a common component that could contain the allergen responsible for the reaction.
2. Treatment for an adverse event requires drugs that would be contraindicated following the vaccine administered. For example, thrombosis with thrombocytopenia syndrome (TTS) has been identified as a complication of adenovirus vectored COVID-19 vaccines.[16,17] Treatment of serious thromboses usually involves administration of heparin, but heparin has been considered to be contraindicated in patients with TTS until heparin-induced thrombocytopenia, which closely resembles TTS, has been ruled out.[18] However, some experts have called for reconsideration of this issue, especially in resource poor environments where alternative drugs are not available.[19]
3. Participant needs protection against the target disease when alternative vaccines are authorised. For example, WHO recommended that study participants at high risk be allowed to unblind and receive COVID-19 vaccines when they became available.[20] The need to provide high risk participants with vaccines as they become available for other diseases should be addressed ahead of time with the appropriate regulatory agencies and the mechanism for doing so specified in the protocol.
4. A participant experiences psychological distress and wants to be unblinded. Several experts shared instances during the COVID-19 pandemic of unusual psychological distress in study participants where decisions were made to allow unblinding to help with the clinical management of the participant.
5. Participant needs documentation of receipt of an available and approved comparator vaccine against the target disease for travel, school, work, military or other activities during a pandemic not foreseen at the time of enrolment.
6. Reporting to regulatory authorities. Most sponsors unblind all serious adverse events for reporting to regulatory authorities. Some sponsors have had unblinding of individual participants by a separate individual or committee without providing the information to the study team unless further action is indicated.[21]

There are several potential problems in dealing with requests for unblinding. Unblinding a single participant for an adverse event may change behaviour in other participants or increase participant drop-outs if the information is publicized; this can be amplified with the widespread sharing of experiences by trial participants on social media.[22] Unblinding may also result in trial investigators over-interpreting clinical symptoms in other participants leading to pseudo-unblinding of those participants.[4] Unblinding or pseudo-unblinding (where participants or investigators believe that they know which product was administered) could result in changes in risk behaviour that could affect the study outcomes. For example, participants who assume that they received a vaccine because of local or systemic reactions may be more likely to engage in risky behaviors than participants who do not.

The procedures surrounding unblinding for individuals with adverse events in vaccine trials are not standardized and consider-

able variability exists. Unfortunately quantitative and qualitative data are not available regarding the reasons for unblinding since these data are not routinely included in publications of trial results. In addition, the roles of DSMBs and SMCs in the unblinding process have not been standardized. ICH guidelines have provided means for site investigators to unblind participants for urgent safety reasons, but this has led to inconsistency in unblinding criteria and negative trial publicity.[23,24] If unblinding of an individual trial participant is not done for the individual's benefit, but to decide whether the adverse event, if causal, is sufficiently concerning to stop recruitment, this should be a concern of the DSMB and should require their involvement in the decision to unblind. The authors and most experts agree that involving the DSMBs and/or SMCs in individual unblinding questions is preferred and should be part of the pre-study training for clinical investigators to maintain trial integrity. Although sponsors are responsible for promptly responding to requests for unblinding selected adverse events, systems should be established to obtain timely input from DSMBs or SMCs before breaking the blind.[25,26]

3. Conclusions

Establishing clear standard operating procedures and careful training of everyone associated with vaccine trials in unblinding criteria and procedures can minimize problems associated with unnecessary unblinding. Regulatory guidance for trials should be improved by distinguishing guidance for vaccines from drugs, with the recognition that unblinding individual participants in vaccine studies is rarely needed for management of adverse events following immunization. The guidance should include establishing specific standard operating procedures to make unblinding more consistent across sites and studies.

Data availability

Data will be made available on request.

Declaration of Competing Interest

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Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.vaccine.2023.04.033>.

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